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INSIDE

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Information and Inspiration, London 2005

By Philip R. Fischer MD, DTM&H

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Dr. Fischer reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company having ties to this field of study.

Gray skies, warm collegiality, professional education, and personal inspiration—it was all available in London. On November 10-11, 2005, 150 travel medicine practitioners from 30 countries gathered at the Royal College of Surgeons for a travel medicine conference sponsored by the *Journal of Travel Medicine and Infectious Disease*. Detailed proceedings will be published by the *Journal* in an upcoming issue, and should include key reviews of information resources, vaccination, tick-borne diseases in travel medicine, pediatric travel, emerging infections, and urban risks of travel. In the meantime, however, discussion of several other important points is already of interest to *Travel Medicine Advisor* readers.

Update on Regulations

Since 1969, the World Health Organization's International Health Regulations has governed vaccine requirements for foreign travelers. The goal of this legal document is to limit the spread of disease. (Evidence-based recommendations to guide clinical care are found in another WHO publication, *International Travel and Health*.) Now, a new edition of the Regulations has been approved.

What changes can be anticipated as the new document and its regulations are implemented in 2007? There will still be yellow fever vaccine centers, but there will be fewer restrictions on who can provide the vaccine and accompanying certificate. The certificate will also be reformatted to allow entry of more customized vaccine information, and health workers other than physicians will be permitted to officially sign the document. However, unvaccinated individuals, even if vaccine was contraindicated, can potentially be quarantined for 6 days upon arrival from a yellow fever endemic area.

Immunizations

Hajj: Two million Muslims from 140 countries converge on Mecca each year in fulfillment of one of the pillars of Islam. Scheduled by the lunar calendar, Hajj trips are currently winter-time expeditions. There has been con-

siderable recent press about the need for quadrivalent meningococcal vaccine and polio vaccine coverage for travelers going on the Hajj. A British health group working both in the UK and Saudi Arabia identified a high rate of respiratory infections among several hundred British pilgrims during the 2005 Hajj. Studies in clinics and tent camps, though somewhat biased toward those who were symptomatic, identified influenza in 14% of individuals (influenza A in 10% and influenza B in 4%). In addition, 3% had RSV. Influenza vaccine should be strongly considered for travelers of any age going on the Hajj.

Rotavirus: Children with diarrhea in Botswana were tested for various viral pathogens from 1999 to 2002. Of 595 individuals, 13% had rotavirus (89% of these were less than 2 years of age) and 3% had astrovirus. New rotavirus vaccines are looming on the horizon, and clinical indications have not been fully determined. If vaccination is not universal for children in North America, one wonders if foreign travel might become an indication for vaccination of traveling children.

Hepatitis A: In the Netherlands, outbreaks of hepatitis A are typically seen following the summer holiday when children of Dutch immigrant families return from family visits to the countries of their ancestral origin (often Morocco and Turkey). During the past 8 years, pre-holiday vaccination campaigns have resulted in a 50% drop in the overall incidence of reported cases of hepatitis A in Amsterdam. (Concurrently, at least one American advisory group has suggested that hepatitis A vaccination be provided to all American 1-year-olds.)

Traveler's Diarrhea

Population-Based Data: For years, we have heard that traveler's diarrhea is common (30-40%) among travelers to developing countries. How important is this to local populations? Reviewing 30 general practices involving 215,000 residents of Wales over 3 years, a population-based study showed that traveler's diarrhea prompted medical consultation in 15 people per 100,000 population each year.

Resistant Campylobacter: Does the presence of blood in stool affect diagnostic thinking? Should it? In a Spanish travel disease facility, 6% of patients presenting with diarrhea over 19 months had bloody stools. Campylobacter was the most frequently identified pathogen overall and, was similarly, frequently seen whether the diarrhea was bloody or not. However, ciprofloxacin resistance was more frequently noted when the Campylobacter came from a patient without bloody stools (97% vs only 40% of those with bloody stools).

Malaria

Got Prophylaxis? Malaria is still commonly seen among travelers returning to Portugal. Of 109 cases in one hospital, most had not taken prophylactic medications, and had falciparum malaria following travel to Africa. Fortunately, no deaths were noted in this series.

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Common Things are Still Common: Post-mortem samples from 5 patients were sent to the CDC for analysis of presumed bacterial infection or viral hemorrhagic fever. Using novel technology and samples of heart, lung, and brain tissue, a post-mortem diagnosis of malaria was made in 4 of the 5 patients. Even when initial evaluation for malaria is negative, critically ill febrile patients returned from malarial areas should still be suspected of having malaria.

No Resistance: Genetic testing of cytochrome B mutations in *P. falciparum* from the Thai-Myanmar border area was negative in 27 patients. Despite the increased use of atovaquone-proguanil in this area, atovaquone resistance does not seem to have emerged yet.

Poor Compliance > Resistance: In France, analysis of 10 cases of apparent atovaquone-proguanil-resistant malaria turned out to reveal true resistance in just 2—others had failed to respond to treatment due to poor compliance, vomiting, or poor absorption. When resistance was identified, it emerged with drug pressure—thus later recurrence of symptoms should prompt consideration of emerging mutations with resistance.

Eat Fat? A case of presumed resistance to artemether-lumefantrine in Belfast turned out to be due to inadequate absorption. It was postulated that taking this combination treatment with fatty foods would improve absorption and outcomes.

Conversation Starters

Warthogs: A study of Tanzanian animals showed that 10% of warthogs were infected with sleeping sickness, whereas only 1% of cows were infected. Watch out for sharing tsetse flies with warthogs!

Compliance: A case of Japanese encephalitis in an American student following travel in Thailand prompted a review of compliance with pre-travel advice in the case individual's 22 co-travelers. Only half had been advised by a health care provider to avoid insect bites prior to the trip. Nonetheless, 75% used repellents at least some of the time. Rare cases might serve to fortify our pre-travel advice and, potentially, travelers' compliance with advice.

Inspiration?

A keynote speaker reminded conference participants that 19th century literary figure WB Yates said that "Education is not the filling of a pail, but the lighting of a fire." Participants at the London travel medicine conference did indeed get their information pails filled. At the same time, however, they networked and interacted in ways that could light their fires for the ongoing practice of travel medicine at their home sites. ■

Malaria in Long-Term Travelers

By Lin H. Chen, MD

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Dr. Chen reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company having ties to this field of study.

At the 54th annual meeting of the American Society of Tropical Medicine and Hygiene held in Washington, DC, on December 11-15, 2005, a symposium was devoted to Malaria in Long-Term Travelers, with Drs. Monica Parise, Patricia Schlagenhauf, and Alan Magill as guest speakers. The clinical pre-meeting course, Anti-Malaria Chemoprophylaxis, also included a presentation by the associate editor on Prevention of Malaria in Long-Term Travelers. Travel Medicine specialists face many questions associated with long-term travel. Most existing guidelines, including those of the US Centers for Disease Control and Prevention, focus on preventing malaria in the short-term travelers. What is the risk of acquiring malaria with long stays? Are drugs for malaria chemoprophylaxis safe for long-term use? What are the strategies travelers actually adapt? What is the possibility of harboring hypnozoites from *P. vivax* (and to a lesser degree, *P. ovale*) that may later cause relapses, especially following a long stay in risk areas? Is there a role for presumptive anti-relapse therapy in such travelers (PART, also known as terminal prophylaxis)?

There is currently no consensus on the definition of long-term travel. However, UK guidelines, written by Hughes and colleagues on behalf of the Advisory Committee on Malaria Prevention, regarded travel for > 6 months as long-term.[1] Long-term travelers may include urban expatriates and diplomats, as well as missionaries, rural expatriates, field researchers, Peace Corps volunteers, students, and backpackers; thus, their risks may vary greatly from one another. Available data show that the risk of acquiring malaria increases as the stay is prolonged.[2,3] At the same time, data show that the use of personal protective measures (long clothes, air-conditioning, repellents, insecticides, mosquito nets, coils) is simply abysmal.[4,5]

Table 1

Reasons for Discontinuation of Continuous Chemoprophylaxis

Adverse events from medication
Inadequate medication—counterfeit or lack of quality assurance
Fear of long-term side effects
Complicated or daily regimen
Inconsistent advice
Misdiagnosis—distrust chemoprphylacxis
Breakthrough malaria—lose confidence in chemoprophylaxis
Misperceptions about malaria—trivialization of malaria infection

Anecdotally, many long-term travelers abandon continuous chemoprophylaxis. One of the reasons cited for discontinuation is the fear of potential side effects from chemoprophylaxis drugs, although other reasons also contribute to discontinuation of chemoprophylaxis. (*see Table 1*) In the United States, doxycycline is labeled for up to 4 months of continuous use as malaria chemoprophylaxis. Otherwise, there is no specific restriction on the duration of use in the label of chloroquine, hydroxychloroquine, mefloquine, atovaquone-proguanil, or primaquine. There is some variation in other countries' guidelines, and confusion may arise when a traveler is overseas. The safety of malaria chemoprophylaxis in clinical trials provides some reassurance, as shown in *Table 2*.

Nonetheless, many travelers choose to take chemoprophylaxis intermittently or only during the high transmission season, or rely solely on standby emergency treatment (SBET, also referred to as emergency self-treatment). While these alternative strategies may be acceptable in certain geographic regions with very clearly defined transmission seasons, they are inappropriate for most of sub-Saharan Africa, which is felt to generally have high levels of transmission. Note that SBET has been recommended by the World Health Organization since 1988 for travel to certain destinations: areas with low malaria transmission but without reliable diagnostic and therapeutic facilities (parts of SE Asia), high risk areas for *P. falciparum* where chemoprophylaxis drugs may not be effective, and remote areas, to be prescribed along with chemoprophylaxis (parts of East and Central Africa).[6]

The new Swiss-German-Austrian guidelines for malaria chemoprophylaxis have shifted to favor SBET, a move considered by many experts to be bold. These new guidelines continue to recommend continuous chemoprophylaxis for high-risk areas including sub-Saharan Africa, some provinces in Brazil, Indonesia, and Oceania. In other regions, the Swiss-German-Austrian guidelines recommend SBET with chloroquine, mefloquine, or atovaquone-proguanil or artemether-lumefantrine, based on the resistance patterns. The argument for the change in recommendations is that the benefit of chemoprophylaxis should be > 10 times greater than the risk of adverse events. The results from this shift in Swiss-German-Austrian recommendations may help to guide future strategies for malaria prevention, and may especially benefit long-term travelers. For now, SBET should be considered in addition to continuous chemoprophylaxis for most long-term travelers.

Finally, some studies have shown that *P. vivax* causes from one-quarter to over one-half of malaria cases in travelers.[7,8] *P. vivax*, along with *P. ovale*, have dormant liver stage parasites called hypnozoites that may cause relapses. Primaquine is the only causal prophylaxis against the hypnozoites, whereas chloroquine, mefloquine, doxycycline, and atovaquone-proguanil are only suppressive prophylaxis. Primaquine is indicated as primary anti-malaria prophylaxis, radical cure, as well as presumptive anti-relapse therapy (PART, or terminal prophylaxis). For long-term travelers, primaquine may be especially useful for the following situations: long stay in areas with high-risk for *P. vivax*, stay in low-risk areas with intermittent visits to areas with high-risk for *P. vivax*, and as PART in combination with other chemoprophylaxis regimen to be administered after departing from *P. vivax* risk areas. It may also be used for travelers

Table 2

Longest Published Clinical Use of Malaria Chemoprophylaxis

Medication	Duration of use	Comment	Reference
Chloroquine	2-3 years	Peace Corps volunteers	9
Mefloquine	2-3 years	Peace Corps volunteers	9
Doxycycline	12 months	Australian Defense Force to Cambodia	10
Atovaquone-proguanil	34 weeks	Post-marketing surveillance	11
Primaquine	52 weeks	Nonimmune Javanese transmigrants to Papua	12

who cannot tolerate other anti-malarials. Testing for adequate levels of G6PD must be done before prescribing primaquine, because life-threatening hemolytic anemia can occur in G6PD-deficient individuals. Although the original FDA approval for primaquine was 15 mg daily for 14 days, the current CDC recommendation is 30 mg daily for 14 days. The higher dose is important for tropical strains of *P. vivax*. Clinicians in the United States need to advise travelers that the use of primaquine as primary chemoprophylaxis is off label.

In summary, prevention of malaria in long-term travelers should be individualized. Guidelines for long-term travelers should be developed such that they are consistent, in order to minimize confusion for the travelers. Travel medicine specialists should emphasize the importance of personal protective measures, particularly for long-term travelers. Continuous chemoprophylaxis along with SBET is the safest strategy for long-term travelers, and travelers should be encouraged to have medication for at least the initial several months. Establishing reliable medical care at destination is crucial in preventing malaria in long-term travelers. With reliable local medical expertise at the destination, long-term travelers may obtain appropriate advice regarding malaria and seek timely treatment if necessary. ■

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Measles Importation: Coming Soon to a Neighborhood Near You?

ABSTRACTS & COMMENTARY

By Frank J Bia, MD, MPH

Synopsis: *No sooner had the CDC's December 9, 2005 issue of* Morbidity and Mortality Reports *hit mailboxes and library shelves when New York City announced the arrival of a 12-month-old child at Kennedy Airport on December 17th with clinical measles. The numbers of acute measles cases in the United States may be reaching new lows, but the proportional contribution of imported measles, often in children who were traveling unprotected while visiting friends and relatives (VFRs), remains nearly 50%. The recent New York City experience highlights the issues which impinge directly upon those of us involved in the practice of Travel Medicine.*

Sources: CDC. Measles—United States; 2004. *MMWR Morb Mortal Wkly Rep*. 2005;54:1229-1231; Gillian YA, Zucker JR. Imported Case of Measles on a Flight from Bangladesh. nyc.gov/health. 2005 Health Alert #48, December 29, 2005.

THE BIMAN BANGLADESH FLIGHT FROM DHAKA TO JFK airport that arrived on December 17th was carrying a 12-month-old child with infectious measles. This young child from Queens county had not been vaccinated against measles prior to departure. Recall that travel recommendations for infants who are 6-12 months of age and are traveling to a measles endemic region call for measles vaccination. Patients who have measles are known to be infectious for 4 days before and after the onset of the rash. While in Bangladesh, she had been diagnosed clinically with measles on the basis of a rash with its onset on December 15th. Blood drawn on

December 21st was serologically positive for both IgM and IgG antibodies. Virus isolations from urine and nasopharynx are still pending. Both parents and an older sibling had been vaccinated against measles.

COMMENTARY

The CDC report on measles in the United States for 2004 estimated the measles incidence level at less than one case per million population, and only 37 cases were reported for that year. This figure also represents a 16% decrease from the previously reported low of 44 cases in the year 2002. However, hidden in these relatively low incidence rates are important lessons for those of us who are travel medicine providers. Fully, 33 (89%) cases were importation-linked, and two-thirds of these could have been prevented if ACIP recommendations regarding measles vaccination of foreign travelers had been followed. Three states, Washington, California, and New York, accounted for nearly half the cases reported in 2004. Of these 37 cases, fully 27 (73%) were imported. These 27 imported cases were nearly equally split between foreign nationals traveling from abroad to the United States and US residents who acquired measles infection while traveling abroad (essentially, VFRs). The origins of these cases were skewed towards China (13), India (4), Bangladesh (2), and Thailand (2). Nearly half of the 27 cases were infectious during their airline flights. A single passenger who had been seated next to a person with infectious measles at the time was infected as a result of virus transmission during the flight, despite having a history of having previously received 2 doses of measles-containing vaccine at some point. The CDC had determined that all 14 US residents had been eligible for measles vaccination prior to exposure. In addition, of the 13 imported cases documented among non-US residents, 10 were unvaccinated and the other 3 had an unknown vaccination status.

There were 2 measles outbreaks in the United States during 2004. One represented imported cases from China among adoptees arriving in 3 states, and they resulted in one secondary case. In a second instance, a 19-year-old US student was infected in India, and his infection resulted in 2 secondary cases. One occurred in a patient who had been seated next to the student on an aircraft. Measles is highly infectious, and the potential for transmission on intercontinental flights would appear to be high. However, from 1996 to 2004, 117 patients with imported measles were deemed infectious during aircraft travel in which approximately 10,000 passengers were involved. Four secondary cases occurred and CDC investigators have speculated that the high level of immunity among largely adult passengers, perhaps coupled with vertical airflow patterns in aircraft, lowered the potential for secondary cases.

This is not the first time New York has dealt with imported measles from Bangladesh. In 2004, measles importation resulted in 2 outbreaks in Brooklyn and the Bronx. In Brooklyn, a 9-month-old girl returned from a 3-month trip to Bangladesh with diarrhea and fever. Several office and emergency room visits transpired until her rash appeared and she was diagnosed, during which time, 93 persons were exposed. A second case occurred in a 13-month-old who returned to the Bronx following a 3.5-month visit to Bangladesh. During 2 pediatric emergency department hospital visits, a total of 211 children were exposed to the index case.

The point is to underscore the potential for measles acquisition and spread as a result of importation, and much of that importation will occur as a result of unvaccinated children traveling to endemic areas. Infants who are between 6 and 12 months of age and traveling to endemic areas will not have been vaccinated at this point in their lives.

In general, adults born prior to 1957 are considered immune due to natural infection. They would not require vaccination for measles in preparation for travel. Vaccination is recommended for those adults who were born after 1956 and either were not immunized or received measles vaccines prior to 1980. Adults who have no history of measles diagnosed by a physician or no serological evidence of prior infection are also candidates for measles immunization. Pregnancy and immunocompromised states are relative contraindications to use of this live vaccine, but HIV-infected patients who are not severely compromised are at greater risk from measles than from the vaccine, so they should be considered candidates for immunization.

There is a possibility that children who are seen in travelers' clinics, and are between the ages of 6 months and 12 months, could "fall between the cracks" and become the source of VFR-associated imported measles. Why? Children generally receive their first MMR (live measles, mumps and rubella vaccines) at age 12-15 months, and that is followed by a second dose, separated by at least 28 days. Usually the second dose is given at the time of school entry (age 4-6) or at age 11-12 if not previously administered.[2] However, children between the ages of 6 and 11 months should be on an accelerated schedule for their measles vaccine, which is given in the following manner. They should receive a single dose of monovalent measles vaccine prior to departure for an endemic region, and pick up on the standard schedule when they return from their trip, or while abroad if the stay is an extended one. Often monovalent measles vaccine is not readily available, but MMR can be substituted. The unavailability of monovalent measles vaccine does not preclude measles vaccination for such infants. ■

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Current Strategies in the Management of Leptospirosis

CONFERENCE COVERAGE

By Mary-Louise Scully, MD

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Dr. Scully reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company having ties to this field of study.

DRS. CLINTON K. MURRAY AND DUANE R. HOSPENTHAL convened a symposium on current strategies in the management of leptospirosis at the recent Annual Meeting of the American Society of Tropical Medicine and Hygiene in Washington DC, December 11-15, 2005. Dr. Joseph Vinetz began the symposium with an overview of the epidemiology of leptospirosis. Leptospirosis is a zoonosis caused by pathogenic spirochetes of the genus Leptospira, of which there are over 200 serovars. Leptospirosis is maintained in nature by chronic renal infection of carrier animals that excrete the organism in their urine, thus contaminating the environment. Rodents and small mammals are the most important reservoirs, but livestock and companion animals, such as dogs, can also serve as sources of infection for humans. Human infection occurs through direct or indirect contact with urine or tissues of infected animals. Traditionally, leptospirosis has been a sporadic disease of various rural and tropical settings, usually in persons with specific risk associations, such as veterinarians, farmers, abattoir, and sewer workers. Some recent outbreaks have been associated with adventure tourism and certain water-associated recreational activities, such as the Eco-Challenge and Triathlon participants.[1,2]

However, leptospirosis is increasingly recognized as a major urban pathogen capable of significant epidemic activity in Latin America. Dramatic urban population growth in places such as Brazil has resulted in the creation of urban slums (favelas), with poor sanitation and rodent infestation. Annual epidemics occur in these areas after seasonal heavy rainfall and flooding. In Brazil alone, approximately 10,000 cases are reported each year from all major cities, with mortality of 10-15%. However, mortality can climb to over 50% in patients who develop severe pulmonary hemorrhage, now recognized as a presentation of severe disease acquired in urban areas. In a recent study from Iquitos, Peru, of 633 febrile patients, 50.7% had serologic evidence of acute leptospiral infection. Seven patients had severe pulmonary manifestations, and 5 of these patients died. Severe cases were associated with urban as opposed to rural exposure and certain Leptospira serovars may be more virulent than others. High levels of leptospiremia as detected by PCR were present in most fatal cases, implying an inoculum effect may also contribute to the development of more severe disease.[3]

The urgent need for the development of new serodiagnostic tests to differentiate leptospirosis other acute illnesses in the tropics was next discussed by Dr. Albert Ko. Leptospirosis may not be high in the differential diagnosis until more classic manifestations, such as fever, jaundice, and renal failure develop (known as Weil's disease). The standard serologic test, the microscopic agglutination test (MAT), is performed mostly in reference laboratories and often requires paired sera, making it less helpful for rapid diagnosis. Similarly, the long delay of traditional culture isolation techniques limits its usefulness to the clinician. Some whole-cell leptospiral antigen preparations have been developed but can have less than 70% sensitivity in the first week of illness. Sensitivity increases after 7-10 days, so a second sample should be taken again if the diagnosis is still in question. The use of recombinant Leptospira antigen-based ELISAs has been investigated as well.[4] More recent work with leptospiral immunoglobulin-like repeat (Lig) proteins shows promise as an early diagnostic test, and may be available in the near future.

The use of antimicrobial agents for leptospirosis was addressed by Dr. Clinton Murray. To assess the increasing array of antibiotics potentially useful for treatment of leptospirosis, he and colleagues developed an in vitro microdilution technique which is more efficient at evaluating a greater number of antimicrobial agents and *Leptospira serovars* than the traditional macrodilution tests. Many antimicrobials were found to have in vitro activity against Leptospira including traditional antileptospiral drugs, such as penicillin G, doxycycline, and ceftriaxone but also erythromycin, clarithromycin, telithromycin, cefepime, and imipenem-cilastatin.[5] A hamster model of leptospirosis also showed efficacy of various agents including doxycycline, azithromycin, and telithromycin. In related data presented in an abstract, telithromycin produced a 98% survival against a lethal

challenge in the hamster model of acute leptospirosis.[6] Although it is unlikely these newer, more expensive agents will supplant the use of less expensive medicines, such as penicillin or doxycycline in developing countries; the information on the newer macrolides and ketolide agents is useful. Clinical trials of antimicrobial agents are mostly limited to penicillin, doxycycline, cefotaxime, and ceftriaxone. A randomized, controlled trial in Thailand demonstrated doxycycline and cefotaxime to be satisfactory alternatives to penicillin G for the treatment of severe leptospirosis.[7] In addition, ceftriaxone was found to be as effective as penicillin for the treatment of acute, severe leptospirosis.[8] The advantage of once daily dosing and the possibility of intramuscular administration are 2 advantages of ceftriaxone over penicillin.

Wrapping up the symposium, Dr. David Haake presented the latest work on vaccine development, an area that has been challenging. The work on a subset of outer membrane proteins exposed on the surface of a bacterial cell (the surfaceome) is the focus of recent efforts. Some of these proteins include LipL32, LipL21, LipL41, and OmpL1. Also, the leptospiral immunoglobulin-like (Lig) proteins such as Lig A and Lig B, whose induction may be influenced by osmolarity, are potential vaccine candidates.[9] Although only partial protection has been achieved to date, it is hoped that these various outer membrane proteins hold promise as vaccine candidates, in that they are relatively well conserved across the pathogenic species of Leptospira. ■

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CME Questions

1. Resistance is commonly reported in which of the following situations?
- a. Malaria to atovaquone-proguanil
- b. Malaria to artemether-lumefantrine
- c. Campylobacter to ciprofloxacin
- d. Warthogs to sleeping sickness
- e. Japanese encephalitis virus to currently available vaccines

2. For long-term travelers, primaquine may be especially useful *except* during which of the following situations?
- a. Long stays in geographic areas with high-risk for *P. vivax* infections.
- b. A stay in low-risk areas with intermittent visits to areas with high-risk for *P. vivax*.
- c. Intermittent prophylaxis in areas where *P. falciparum* infections predominate.
- d. As PART (presumptive anti-relapse therapy or terminal prophylaxis]) in combination with other chemoprophylaxis regimens to be administered after departing from *P. vivax* risk areas.
- e. For travelers who cannot tolerate other anti-malarials.

3. Measles vaccination is indicated for the following travelers to endemic regions *except* which group(s)?
- a. All unvaccinated adults who were born prior to 1956.
- b. Adults, who were vaccinated between 1957 and 1980, with no history of clinical measles.
- c. Infants between ages 6-12 months, traveling to measles-endemic areas.
- d. Non-immune pregnant women traveling to endemic areas for measles.
- e. HIV-infected adults who are not severely immunocompromised.
- f. A and D

4. Which one of the following statements regarding human Leptospirosis is *true*?
- a. Treatment with penicillin is superior to other antibiotics.
- b. Infection is caused by human contact with sick poultry.
- c. Rapid diagnostic tests are highly sensitive during early illness.
- d. Disease outbreaks are generally limited to rural areas of Latin America.
- e. Leptospirosis can be associated with severe pulmonary manifestations including hemorrhage.

Answers: 1. (c); 2. (c); 3. (f); 4. (e)

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.

Letrozole for Postmenopausal Women with Breast Cancer

Letrozole (Femara) is a potent aromatase inhibitor that is used to treat women with metastatic breast cancer and, in a neoadjuvant role, for women who have failed tamoxifen. Aromatase inhibitors exert their effect by blocking the conversion of androgens to estrogens and reducing estrogen levels in tissue and plasma. Recently, letrozole was compared with tamoxifen for adjuvant therapy in postmenopausal women with steroid-hormone-receptor-positive breast cancer.

A total of 8010 women were randomized to 5 years of letrozole (4003) or tamoxifen (4007). After a median follow-up of 25.8 months, there were 351 events (local or distant recurrence) in the letrozole group and 428 events in the tamoxifen group, with 5-year disease-free survival estimates of 84% and 81.4%, respectively. Adverse effects of the drugs were different with tamoxifen, resulting in a higher rate of thromboembolism, endometrial cancer, and vaginal bleeding, while letrozole was associated with a higher incidence of skeletal and cardiac events and hypercholesterolemia.

The authors suggest that in women with endocrine-responsive breast cancer, adjuvant treatment with letrozole, as compared with tamoxifen, reduced the risk of recurrent disease (Thurlimann B, et al. A Comparison of Letrozole and Tamoxifen in Postmenopausal Women with Early Breast Cancer. *N Engl J Med*. 2005;353:2747-2757). In an accompanying editorial Sandra Swain, MD, from the National Cancer Institute, states that "all the evidence points to aromatase inhibitors as critically important for improving the outcome among postmenopausal women with breast cancer who have positive or negative lymph nodes and who are at a substantial risk for recurrent disease." (Swain SM, et al. Aromatase Inhibitors—A Triumph of Translational Oncology. *N Engl J Med*. 2005;353:2807-2809). Based on this study, the FDA has recently approved letrozole for adjuvant treatment (immediately after surgery) in postmenopausal women with hormone sense of breast cancer.

Do Antidepressants Increase Risk of Suicide?

An article in the January issue of the *American Journal of Psychiatry* asks "Is the FDA Warning About Antidepressants Wrong?" Researchers from Group Health Cooperative in the Pacific Northwest used population-based data to evaluate the risk of suicide death and serious suicide attempt in relation to the initiation of antidepressant treatment.

Computerized health plan records for over 65,000 patients with over 82,000 episodes of antidepressant treatment between 1992 and 2003 were reviewed. In the 6 months after initiation of antidepressant treatment, the risk of suicide was found be no higher than at any other time during treatment. The risk of suicide attempt was highest in the month before starting treatment, and declined progressively after starting medication. When newer drugs were compared to older drugs, an increase in suicidality was

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only seen with the older drugs.

The authors conclude that the risk of suicide during acute-phase antidepressant treatment is approximately 1 in 3000 treatment episodes, and the risk of serious suicide attempt is approximately one in 1000. Available data do not indicate significant increase in risk of suicide or serious suicide attempt after starting treatment with newer antidepressant drugs (Simon GE, et al. Suicide Risk During Antidepressant Treatment. *Am J Psychiatry*. 2006;163:41-47, available free at ajp.psychiatryonline.org). The study calls into question the March 2004 FDA public health advisory regarding worsening depression and suicidality in pediatric and adult patients being treated with 10 newer antidepressants (bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, escitalopram, and venlafaxine).

Can Viagra Improve Heart Function?

Concern still lingers regarding the safety of erectile dysfunction drugs in patients with heart failure. A new study from Australia suggests that sildenafil (Viagra) actually improves heart function in patients with systolic dysfunction. In a randomized, placebo-controlled, double-blind, 2-way crossover study, 20 patients with controlled left ventricular failure and ejection fractions < 35% received sildenafil 50 mg or matching placebo. Cardiac output was determined by Doppler echocardiography, aortic pressure waveform, and aortic and femoral arterial stiffness was also evaluated. With a peak effect at 60 minutes after administration, sildenafil resulted in an increase in cardiac index of 0.37 L/min, decrease in total systemic resistance, decreased aortic and lower limb pulse-wave velocity, and decreased wave reflection (all significant at $P < .0001$). The authors conclude that sildenafil improved cardiac performance by decreasing LV load, resulting in increased cardiac output and increase in exercise capacity in heart failure patients (Hirata K, et al. Effect of Sildenafil on Cardiac Performance in Patients with Heart Failure. *Am J Cardiol*. 2005;96:1436-1440).

Can Tamoxifen Increase Your Height?

Tamoxifen may increase height potential in short pubertal periods, according to new study in the journal *Pediatrics*. The study was a retrospective chart review of 7 boys with a mean age of 15 who took tamoxifen 10-20 mg twice a day for a mean of 26 months. Six of the boys were also receiving growth hormone. Tamoxifen significantly decreased the rate of skeletal maturation and improved predicted adult height without negative effects on sexual maturation. Skeletal maturation was determined by review of bone radiographs by independent endocrinologists. The authors state that "additional evaluation of this therapy is now required to determine if the increase in predicted adult height results in a clinically significant increase in final adult height." (Kreher NC, et al. The Use of Tamoxifen to Improve Height Potential in Short Pubertal Boys. *Pediatrics*. 2005;116:1513-1515).

A Dramatic Increase of Clostridium difficile

Clostridium difficile is increasing in frequency and severity in both hospital and community settings. Widespread use of acid suppressing proton pump inhibitors (PPIs) and H2 receptor agonists (H2RAs) may be a contributing factor, according to new study. Two population-based, case-control studies from England reviewed all 1672 cases of *C. difficile* reported between 1994 and 2004, while a second study looked at cases defined as community acquired. All cases were matched 10 controls. The incidence of *C. difficile* increased dramatically between 1994 and 2004. The adjusted rate ratio of *C. difficile* associated disease with current use of PPIs was 2.9 (95% CI, 2.4-3.4) and, with H2RAs, the rate ratio was 2.0 (95% CI, 1.6-2.7). The authors conclude that the use of acid-suppressive therapy is associated with an increase risk of community-acquired *C. difficile*. Parenthetically, they also found an increased risk associated with use of nonsteroidal anti-inflammatory drugs (*JAMA*. 2005;294:2943-3048).

FDA Actions

The FDA has approved Bristol-Myers Squibb's abatacept (Orencia) for the treatment of rheumatoid arthritis. The drug, which is produced by recombinant DNA technology, is a T cell costimulation modulator. It is approved for patients with moderately-to-severely active rheumatoid arthritis who had an inadequate response to one or more DMARDs, including TNF antagonists. It may be used as monotherapy or with other non-TNF inhibitor DMARD. Abatacept is administered as a 30-minute IV infusion at 0, 2, and 4 weeks, then every 4 weeks thereafter.

The FDA and GlaxoSmithKline have issued a "Dear Doctor" letter regarding rare reports of macular edema in patients receiving rosiglitazone (Avandia). The majority of the cases involved concurrent peripheral edema and, in the majority of cases, macular edema improved with discontinuation of the drug. Macular edema presents as blurred or distorted vision, decrease color sensitivity, and decreased dark adaptation. ■