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Malaria Prevention and Travel Vaccines Updates from CDC at Society Meeting

Special Report

By Lin Chen, MD

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

At the 56th annual meeting of the American Society of Tropical Medicine and Hygiene held Nov. 4-8, 2007, in Philadelphia, Paul Arguin, MD, Chief of the Domestic Malaria Unit at the Centers for Disease Control and Prevention, presented the Malaria Prevention Update from the CDC. He covered the following topics: 1) preliminary data from 2006 malaria surveillance; 2) rapid diagnostic tests; 3) recent outbreaks (Jamaica, Bahamas); 4) malaria maps; 5) artesunate availability in the United States; 6) e-mail updates.

The preliminary data showed approximately 1,400 cases of malaria reported to the CDC in 2006. Of those, 60% occurred in U.S. civilians, 20% in foreign civilians, 6% in military personnel, and 14% were in persons of unknown category. Among the U.S. civilians, main species of malaria were *Plasmodium falciparum* and *P. vivax* (41.3% and 22.0%, respectively). Countries where the exposures occurred most frequently were Nigeria, India, Ghana, Afghanistan, Uganda, and Sierra Leone. Among the foreign visitors, the most common countries where patients acquired malaria were India, Nigeria, Ghana, and Cameroon. The most frequently cited reason for travel was VFR (47.1%). There were six deaths attributed to malaria: five cases of *P. falciparum* (acquired in Ghana, Nigeria, Kenya, Uganda), and one case of *P. malariae* (acquired in Thailand).

Dr. Arguin reported on the FDA approval of BinaxNOW Malaria, a rapid diagnostic test for malaria, which may become very useful in decreasing the time to diagnosis of malaria (see the October 2007 issue of *TMA* Updates for a review of BinaxNOW Malaria). He then discussed the recent malaria outbreaks in Jamaica and Bahamas. The first case of malaria in the United States associated with travel to Jamaica occurred in a 44-year-old woman VFR traveler, who had lived in New York for 12 years. She visited Jamaica from Oct. 29 to Nov. 6, 2006, and developed symptoms on Nov. 20, 2006. She was diagnosed with *P. falciparum*, and responded to chloroquine. This case was associated with an outbreak in Kingston from late 2006 to June 2007 that totaled 370 reported cases. It had appeared that the outbreak was over, but in October 2007, two new cases of malaria were diagnosed along with leptospirosis and dengue outbreaks.

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The CDC again recommended chloroquine for travelers visiting Kingston. The likely source is attributed to a traveler from Haiti.

The Bahamas also experienced two outbreaks of malaria on Great Exuma: one in 2006 and one in 2007. The first outbreak resulted in 19 cases reported from May to June 2006, including four cases occurring in travelers, which led to the recommendation for malaria chemoprophylaxis temporarily. In August 2007, the CDC received reports of malaria in an 18-year-old male traveler, who lived in Florida and had only traveled to the island of Great Exuma. The Bahamas authorities detected one additional case at that time. No new cases have occurred since then, and the CDC planned to rescind the recommendation for chloroquine in November 2007 (this recommendation has been posted as of Dec. 13, 2007).

The CDC has developed malaria maps as a geography tool, where queries on a location will draw up recommendations for malaria prevention for the location. This is being tested at www.cdc.gov/malaria/risk_map/.

Artesunate is now available to treat malaria. In the United States, there are 50-100 cases of severe malaria annually, and 54 deaths occurred from 1999-2006. The CDC is making artesunate available under an IND protocol, and inclusion criteria are: patient with malaria; parenteral medication is required; artesunate is preferred, either because it is more readily available than quinidine, the patient has failed quinidine, is not tolerating quinidine, or if both drugs are equally available and artesunate is preferred by the treating physician. Artesunate has been released by CDC for seven patients to date: average age is 35, range 2 to 58 years of age. Of those, 57% are male, 100% *P. falciparum*; 83% acquired in Africa and 17% in the Caribbean. Eighty percent received it because quinidine was not available, while 20% received it because quinidine was not being tolerated. Most of these cases of severe malaria were associated with significant delay in diagnosis [onset of symptoms to hospital presentation, 5.4 days (3-7)] which is a known risk factor for developing severe disease. The average time from the artesunate request to shipping has been 1 hour (range 0.4-10.8 hours), and the average length of time from the artesunate request to treatment has been 4.3 hours (range 3.5-15.5 hours). One of the patients who received artesunate was subsequently found not to have had malaria. All patients have survived. One patient had a severe adverse event. This patient developed acute renal failure. However, upon review, it was felt that the renal failure was caused by the severe malaria and was not due to artesunate. In summary, parenteral artesunate (IV) is available. The distribution system is working, and the drug is effective. However, thus far it is underutilized. The CDC anticipates request for the drug about once per week. Request the drug from 770-488-7788 during the day and 770-488-7100 after hours, weekends, and holidays.

Additionally, the malaria updates from the CDC are available via e-mail. To subscribe to the free service, go to www.cdc.gov/malaria/ and follow the link on the right side of the screen: "Get e-mail updates."

Nina Marano, DVM, MPH, Branch Chief Geographic Medicine and Health Promotion Branch, CDC, presented the CDC Travel Vaccines Updates. The Advisory

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Committee on Immunization Practices (ACIP) recently recommended hepatitis A vaccine over the single dose of IG for healthy travelers with imminent departure.[1]

In the past, the CDC has recommended the administration of IG for departure within four weeks. However, a study in Kazahkstan found that the vaccine was effective post-exposure in preventing hepatitis A infection.[2] The ACIP also updated recommendations for meningococcal vaccine, where minimum age is now lowered to 2 years of age. Adults may be immunized more than once with the vaccine, and the conjugate vaccine is preferred in individuals 55 years old and younger. In persons who had received the polysaccharide vaccine previously, revaccination is considered after 3-5 years.

Dr. Marano reported on the yellow fever vaccine-associated deaths in Peru (Ica), where four people have died recently following the vaccine. All were first-time recipients who received the vaccines during a yellow fever vaccination campaign, and one patient was reported to have lupus, although investigation is still being carried out at this time.

The CDC conducted an assessment of yellow fever vaccine prescribing practices in the United States, which surveyed pharmacies informally. There were 32 responses from 50 states: 25/32 responded that their state law did not permit dispensing/administering the vaccine, whereas 5/32 stated that they do so under the auspices of a licensed physician and stamp holder.

The new International Certificate of Vaccination or Prophylaxis (ICVP) took effect June 15, 2007. The old certificate is valid for 10 years. Travelers will need new certificates for vaccines administered after Dec. 15, 2007. The CDC had the new ICVP available December 1, 2007, at http://bookstore.gpo.gov.

Finally, Dr. Marano discussed the Beijing Olympics, which will take place Aug. 8-18, 2008, in seven cities. Paralympics will take place Sept. 6-17, 2008, in three cities. An estimated 1,200 athletes from the United States will travel to China for the events. The venues in eastern China are associated with possible concerns for Japanese encephalitis, a flavivirus. This is the leading cause of viral encephalitis in Asia, resulting in 50,000 cases per year. The Biken vaccine that has been used in the United States is no longer manufactured, and a new vaccine manufactured by Intercell is expected to be available in late 2008. This is a two-dose series. In view of the limited availability of JE vaccine and limited risk, the CDC does not anticipate recommending wide immunization of athletes or attendees to the Olympics. Clinicians should consider the anticipated exposure individually.

The Associate Editor thanks Drs. Paul Arguin and Nina Marano for their review and edits of this summary of their reports at the ASTMH meeting. ■

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Primaquine — Finding Its Niche for Malaria Chemoprophylaxis

SPECIAL REPORT

By: Mary-Louise Scully, MD
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Dr. Scully reports no financial relationships relevant to this field of study.

A SYMPOSIUM ON PLASMODIUM VIVAX (P. VIVAX) malaria was held at the recent annual meeting of the American Society of Tropical Medicine and Hygiene in Philadelphia. Dr. Eli Schwartz of the Sheba Medical Center in Israel presented his experiences with relapsing P. vivax malaria in travelers to the Omo River in southern Ethiopia, a popular destination among Israeli travelers for adventure river rafting. The majority of malaria in sub-Saharan Africa is caused by *Plasmodium falciparum*, but in Ethiopia, 25% to 35% of malaria cases can be secondary to *P. vivax*. In 1998, Schwartz reported that despite appropriate use of mefloquine for prophylaxis, up to 50% of travelers returning from the Omo River trips were infected with *P. vivax*. In nearly all the patients, the first clinical episode occurred greater than three months after exposure.[1]

In a subsequent study of travelers to the Omo River, patients who had used primaquine for malaria prophylaxis were compared to those using doxycycline or mefloquine. Of the 106 travelers who received primaquine, 5.7% developed malaria. By comparison, in the 19 doxycycline recipients, 53% developed malaria, and in the 25 mefloquine recipients, 52% developed *P.*

vivax malaria. It is noteworthy that among the small number of primaquine-failure cases, a higher proportion of *P. falciparum* infection was observed.[2]

Looking beyond Israeli patients, Schwartz and colleagues showed that up to one-third of all reported cases of malaria in both Israel and the United States were late onset *P. vivax* or *P. ovale* that occurred despite adequate use of blood-stage malaria chemoprophylaxis. [3] The key point is that all our commonly used malaria chemoprophylactic regimens (chloroquine, mefloquine, doxycycline, and atovaquone-proguanil) prevent blood-stage infection but do not prevent relapses of *vivax* malaria because they do not eliminate the liver-stage parasites (hypnozoites). Only primaquine is active on liver hypnozoites of *P. vivax* and *P. ovale*, and primaquine is truly the only agent available to prevent late relapses.

In the November 2007 issue of *Journal of Travel Medicine,* Maguire and Llewellyn report a case of *vivax* malaria after six months of daily atovaquone-proguanil in a 22-year-old soldier stationed in Afghanistan.[4] The patient was not compliant with his atovaquone-proguanil upon departure from Afghanistan, but, regardless, late relapse with *P. vivax* would not have been prevented by atovaquone-proguanil. The case highlights the consideration for expanding the role of primaquine as a primary prophylaxis regimen.

Specifications for the use of primaquine were detailed by Dr. Alan Magill of the Walter Reed Army Institute of Research. The current strategy for prevention of *P. vivax* and *P. ovale* relapses include the addition of two weeks of primaquine (after appropriate blood-stage malaria chemoprophylaxis) for travelers with prolonged or intense exposure in *P. vivax* and *P. ovale* areas. The appropriate terminology for this is now presumptive anti-relapse treatment (PART). Patients need to be tested prior to use of primaquine for G6PD deficiency, as primaquine causes acute hemolysis in patients with hereditary forms of G6PD deficiency. Primaquine is contraindicated in pregnancy. Side effects are usually gastrointestinal symptoms, such as nausea and vomiting, that are lessened by its administration with food.

The optimal dose of primaquine appears to be 6 mg/kg (base), not to exceed 30 mg (base) daily, whereas previous recommendations were lower (15 mg base daily). Tropical *P. vivax* strains in Southeast Asia and Papua New Guinea seem to require these higher doses of 6 mg/kg for effective cure of relapse, which prompted the change in the current CDC recommendations. Even at this dosage, the occasional therapeutic failure can occur.

Primaquine used as a primary prophylactic regimen in areas of high *P. vivax* transmission offers the advantage of preventing late relapses. This use is technically off-label, but primaquine (30 mg base daily) can be used starting one day before, each day during, and for seven days after travel to a malaria risk area. The CDC now lists primaquine as an alternative regimen for those patients with special circumstances or patients who are unable to tolerate other antimalarials. The caution to use this regimen first-line is likely appropriate based on the concern about using primaquine as prophylaxis in areas with a high *P. falciparum* transmission rates. Primaquine has only very modest blood-stage activity, so if parasites break through the liver and into the blood, then clinical cases of *falciparum* malaria can occur. This was found to be the case in the Omo River group, where four of the six breakthrough malaria cases in the primaquine group were, indeed, *P. falciparum*. [2]

We are left with the realization that nothing is perfect in the realm of malaria prevention. Travel medicine physicians should make patients aware of the possibility of clinical illness despite suppressive malaria chemoprophylaxis, even months after their trip. Also, a course of presumptive anti-relapse treatment (PART) should be considered if their travel took them to high risk areas for *P. vivax*. Vivax malaria is especially common in India, Indochina, Latin America, and the Philippine, Indonesian and New Guinean archipelagos.[5] Proper clinical decisions will need to take into consideration the specific destination and risk by species to best define the right choice of malaria chemoprophylaxis for each individual traveler. ■

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Waning Vaccine-Induced Immunity to Varicella

ABSTRACT & COMMENTARY

By Jennifer L. Kruse and Philip R. Fischer, MD, DTM&H

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Jennifer Kruse and Dr. Fischer report no financial relationships relevant to this field of study.

Synopsis: Vaccine-induced immunity to varicella wanes over time, suggesting that a second dose of varicella vaccine may improve protection against infection. A second dose is recommended for individuals who previously received a single dose.

Source: Chaves, S.S., et al., Loss of vaccine-induced immunity to varicella over time. *N Engl J Med* 2007; 356: 1121-1129.

THE INCIDENCE OF CHICKEN POX HAS DECREASED dramatically in the United States since implementation of a universal vaccination program in 1995. However, the question of whether or not there is waning immunity to varicella after one dose of vaccine led Chaves and colleagues to investigate the incidence of varicella in individuals vaccinated with one dose of varicella zoster virus (VZV) vaccine between 1995 and 2004.

The Varicella Active Surveillance Project was established by the CDC in collaboration with local and state health departments in 1995 to monitor cases of varicella in three communities: Antelope Valley, CA; Travis County, TX; and West Philadelphia, PA. The data from this active surveillance project were used by the authors to examine several variables related to varicella infection of vaccinated and unvaccinated subjects, including the effect of time since vaccination on the incidence of breakthrough varicella. Breakthrough varicella was defined as a diffuse maculopapular-vesicular rash without another apparent cause that developed more than 42 days after the subject had been vaccinated with VZV vaccine.

From January 1995 through December 2004, 11,356 subjects with varicella were identified. Within this group, 1,080 subjects (9.5%) had an onset of rash more than 42 days after vaccination. The rate of breakthrough varicella increased significantly with each year after vaccination, from 1.6 cases per 1,000 person-years within the first year after vaccination (95% CI, 1.2 to 2.0) to 20.4 per 1,000 person-years five years after vaccination (95% CI, 14.1 to 29.6) and 58.2 per 1,000 person-years nine years after vaccination (95% CI, 36.0 to 94.0).

COMMENTARY

Before the implementation of a universal varicella vaccination program in the United States, chickenpox was an illness that affected almost every U.S. child. Since 1995 the incidence of chickenpox in the United States has decreased dramatically.[1] However, the incidence of varicella outside the United States remains high, as few countries routinely immunize children for varicella. Several industrialized countries now have universal vaccination programs in place, but most countries must prioritize other public health concerns above varicella or have chosen not to put resources into a universal vaccination program due to reservations about the costs and benefits of vaccination to the individual and the collective. [2] Consequently, most individuals in the world experience disease due to varicella zoster virus at some point in their lifetime. [3]

The epidemiology of varicella in countries without varicella immunization programs varies depending on climate. In temperate climates, most cases of varicella occur before 10 years of age. The epidemiology is less well understood in tropical climates, where a relatively large proportion of adults are seronegative, and disease often presents at a later age.[4] Adults traveling from tropical climates to temperate climates should be vaccinated for varicella if they show no evidence of immunity, as they are more likely to be seronegative and subsequently acquire varicella infection upon travel to temperate climates.

Another consideration in the epidemiology of varicella is the importation of VZV with recent immigrants and/or international adoptees. These individuals may have a varicella infection upon entry to the United States and subsequently serve as a source for varicella outbreaks among susceptible individuals.

Waning vaccine-induced immunity to varicella presents a public health challenge, as it may lead to a pool of susceptible older individuals at risk for more severe disease as a result of their age. It presents a problem for all individuals who have received only one dose of varicella vaccine and presents a particular problem for those within that group who plan to travel internationally. Individuals in the United States have a certain degree of protection due to low incidence of disease and evidence

of herd immunity.[5] However, chicken pox remains a universal childhood illness in most countries, suggesting that individuals with waning immunity to chicken pox who travel internationally are at higher risk of encountering varicella and thus are likely at an increased risk of contracting the disease. Therefore, it is important for individuals who have received just one dose of varicella vaccine to receive a second dose before traveling internationally.

The problem of waning vaccine-induced immunity has been addressed by the Advisory Committee on Immunization Practices, which recommends a routine two-dose varicella vaccination program for children and a second dose catch-up varicella vaccination for individuals who previously received one dose. ACIP also recommends routine vaccination of all healthy adults without evidence of varicella immunity.[6]

The clinical manifestations of varicella include a low grade fever that usually lasts 2-3 days, as well as lesions that begin early and crop up over several days. Because the lesions appear over several days, at any one point in time disparate lesions may be in different stages of development. Lesions appear first on the trunk and head, then move to the extremities including palms and soles, and are frequently found on mucus membranes, conjunctiva, and in the genital region.

The lesions present as papules that become vesiculated. The fluid within the vesicles usually becomes cloudy, and after the vesicles break, the lesions become crusted. The individual is contagious until all lesions have crusted over.

Complications of varicella zoster virus are uncommon but serious, and include secondary bacterial infection, varicella pneumonia, thrombocytopenia, varicella encephalitis, cerebellar ataxia, and Reye's syndrome.

Management of mild disease in otherwise healthy individuals is based on relieving discomfort and may include acetaminophen, antihistamines, and/or local applications such as calamine lotion, cool compresses, or cool baths to calm itching. Due to the risk of Reye's syndrome, it is important to avoid aspirin use in children with varicella. For immunocompromised patients with VZV, acyclovir should be administered, as it has been shown to reduce varicella-associated morbidity and mortality in this population if given within 24 hours of onset of rash. Varicella zoster immunoglobulin is used for prevention of varicella in immunocompromised individuals.[7,8,9]

We have the means to prevent disease due to varicella zoster virus, and we should be vigilant in ensuring immunity in all of our patients in order to protect them and to protect the public from morbidity and mortality due to varicella. All individuals who have not had disease due to VZV should receive two doses of vaccine. Individuals without a history of varicella illness could either undergo serologic testing for possible immunity to varicella, or they could be immunized. In particular, international travelers should receive appropriate immunizations for varicella before traveling. Patients from tropical climates who have no history of clinical chicken pox who are traveling to temperate climates could be immunized against varicella, as they are less likely to have acquired the disease in childhood. And, for patients who are recent immigrants and/or international adoptees, there should be high clinical suspicion for varicella if they present early with rash, as they may have imported a varicella infection that could lead to outbreaks in the community among susceptible individuals. ■

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Requirements for Use of a New International Certificate

Source: CDC. Requirements for Use of a New International Certificate of Vaccination or Prophylaxis for Yellow Fever Vaccine. 2008. *MMWR Morb Mortal* 2008:56;1345-1346.

In response to the 2005 revision of the International Health Regulations (IHR 2005), as of Dec. 15, 2007, a new International Certificate of Vaccination or Prophylaxis (ICVP) has replaced the old certificates.1 The new certificate provides space for potential certification of additional types of vaccination or prophylaxis to protect against newly emerging or reemerging diseases or other events of public health importance. However, the only vaccination currently required to be indicated on the ICVP is for yellow fever.

Yellow fever vaccine is required under IHR 2005 by certain countries for entry, and the new ICVP is required for any yellow fever vaccination administered beginning Dec. 15, 2007. Persons vaccinated before that date may use the old certificate until it expires 10 years from the date of vaccination.

The new certificates are available to health care providers through the U.S. Government Printing Office (GPO). The new ICVPs are available for order from GPO online at http://bookstore.gpo.gov/collections/vaccination.jsp, or by telephone (866-512-1800). Additional information regarding the new requirement is available from the CDC Travelers' Health Team by telephone (404-639-4500) or online via the Travelers' Health web site at www.cdc.gov/travel. ■

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Chagas' Disease Highlights

PRE-MEETING COURSE OF THE ASTMH -2008

Michele Barry, MD, FACP

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Dr. Barry is a consultant for the Ford Foundation and receives funds from Johnson & Johnson.

A clinical pre-meeting course at the 56th annual meeting at ASTMH was conducted and entitled, Chagas' Disease: (American Trypanosomiasis): No Longer an Exotic Disease. Experts from CDC, Brazil, Argentina, in addition to leading researchers in the United States presented a review of diagnosis, treatment and the currently changing epidemiology of the disease. The focus and purpose of the course was to raise consciousness about the rise of imported Chagas' disease into the United States. As the frequency of Chagas' disease decreases in Latin America, with between 8-11 million people infected, the prevalence of infection within the United States is increasing due to immigration; 2003 census demonstrated that 17.9 million people in the U.S. were born in Latin America, many in endemic areas of Chagas' disease. Most recent data on the donated blood supply reveals that blood donors in certain geographic areas of the United States are as likely to be seropositive for Chagas' disease as they are to be seropositive for HIV infection.

Chagas' disease, a zoonotic disease caused by a blood borne parasite is transmitted primarily by triatome insects (i.e. kissing bugs). Infection can also occur via blood transfusion, congenital transmission, organ transplantation, laboratory accident and ingestion of triatome-contaminated food or drink. In the United States, vector-borne transmission of Chagas' disease is rare, although there have been six autochthonous cases reported, half in Texas, where indigenous triatome insects are found.

Chagas' has been identified as a disease infecting humans as long as 9,000 years ago. In a group of 283 mummies from northern Chile and southern Peru, 40.6% were infected with *T. cruzi* when tested with DNA probes for kinetoplast DNA. Of the more than 100 recognized triatomine species, only 10 are widespread colonizers of human dwellings. Examples of these dead insects were actually passed through the class meetingfor examination.

Chagas' disease has an acute stage, typically symptomatic or with mild symptoms; fever, malaise, swelling at the site of inoculation and lymphadenopathy during the first 6 - 8 weeks after infection. If not treated the infection becomes lifelong with low-level intermittent parasitemia. The majority of infected persons remain asymptomatic in a chronic indeterminate phase. However, an estimated 30% will have onset of chronic symptomatic disease, usually decades after the initial infection with cardiac manifestations in particular: dilated cardiomyopathy, apical fibrosis and aneurysms, right bundle branch block, frequent brady- and tachy-arrythmias) or gastrointestinal manifestations such as megaesophagus or megacolon. Typical features described for a U.S. immigrant presenting with Chagas' heart disease were a male between 30 to 50 years of age with childhood residency in Latin America and symptoms of palpitations, a right bundle branch block or right-sided heart failure.

During the ASTMH course four different aspects of the disease were updated: 1) The changing epidemiology in the U.S., 2) changing concepts of clinical manifestations and current treatment, 3) new diagnostic methods and 4) the challenges of the CDC and Red Cross in attempting to prevent transmission of disease through donated blood supply.

Highlights:

1. The changing epidemiology in the U.S. of Chagas Disease

•1916 - the first report of *T. cruzi* in triatomes found within the U.S.

•1983 - first transfusion associated case of Chagas' Disease

•2001 - first case in a transplant recipient

•2006 - U.S. blood banks begin screening for infection with *T.cruzi*

•2007- an estimated 150,000 infected people in the U.S. (approximately 1 in 25 - 30,000 blood donations) seropositive by screening in 2007.

2. Changing Concepts of Clinical Manifestations and Treatment

The concept of parasite persistence in chronic Chagas' disease was reviewed and two competing, but not mutually exclusive, concepts were discussed: disease as the result of over-reactive immune/autoimmune reactivity and disease as a result of persistent parasitic infection. Although acute disease has always been treated, controversy continued as to whether to treat chronic Chagas disease until a recent landmark study by Viotti et al. which demonstrated that treatment of chronic cardiac Chagas' disease with benznidazole slowed rate of disease progression.[1] Dr. Rassi, from Brazil, discussed the pathogenesis of chronic Chagas' cardiomyopathy and argued for treatment of all patients with either nifurtimox (available in United States) or benznidazole, the preferential treatment in Latin America due to less adverse side effects. A definitive, prospective and randomized study of treatment for chronic cardiomyopathy is underway. Dr. Maguire reviewed gastrointestinal disease due to destruction of myenteric Auerbach's plexus. He noted the rarity of gastrointestinal disease in countries north of the equator, with Chile and Argentina reporting the most prevalence of gastrointestinal disease.

3. Diagnostic methods for diagnosing chronic disease

Assay for anti-*T. cruzi* IgG is the recommended approach to diagnosing chronic infections and titers are not related to clinical status or infectivity.

Diagnosis was discussed by Drs. Sosa Estani, Kirchhoff and Tarleton. Examples of serologic test types currently available are ELISA, indirect immunofluorescence (IFA), hemagglutination, complement fixation and radioimmune precipitation assays (RIPA). The procedure for diagnosing chronic Chagas' disease in the United States as of 2007 includes positive serologic reaction on two of three tests. Confirmatory parasitological tests (PCR, blood culture for the causative organism or xenodiagnosis) are rarely performed for chronic disease.

4. New Screening of Blood Donors

For blood donations only, the Ortho *T. cruzi* Elisa test is approved by FDA with RIPA use for confirmatory testing of positive donor samples. Use of donor screening in the United States is not required; however, both the American Red Cross and Blood Systems Inc., organizations, responsible for 65% of the U.S. blood supply, began screening for all donations for *T. cruzi* on Jan. 29, 2007. Unfortunately, undocumented legal status of many positive donors contributes to lack of free treatment of such donors by CDC after being informed of their seropositivity. ■

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CME Questions

1. **Chronic Chagas' disease is diagnosed by which of the following?**
   a) Clinical presentation of right-sided failure in a young man from Bolivia.
   b) Clinical presentation of tachyarrhythmias in a young man from Bolivia with a right-bundle branch block.
   c) All of the above plus positive Ortho *T. cruzi* IgM Elisa test due to reactivation.
   d) A and B plus positive Ortho *T. cruzi* IgG Elisa test and radioimmune precipitation assay (RIPA test).

2. **Which of the following statements regarding CDC malaria surveillance is correct?**
   a) Artesunate will continue to be excluded from available drugs in the U.S. for treatment of severe malaria due to neurotoxicity.
   b) Travel to Great Exuma in the Bahamas currently requires chloroquine prophylaxis for the prevention of malaria in travelers.
   c) Currently travelers to Kingston, Jamaica do not require malaria prophylaxis.
   d) Nearly half of all US travelers who acquire malaria cite "visiting friends and relatives" as their reason for travel.
   e) Severe malaria is most likely associated with geographic origin of infection, as opposed to any delays in diagnosis.

3. **All of the following are true statements about primaquine except:**
   a) Primaquine is contraindicated during pregnancy
   b) Primaquine is the agent of choice for presumptive anti-relapse treatment
   c) Primaquine is very effective for blood stages of P. falciparum
   d) Primaquine is effective against tropical strains of P. vivax when dosed at 6 mg/kg base.
   e) Primaquine is best taken with food.

Answers: 1. d. 2. d. 3. c

CME Objectives

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

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

•To alert the readers to recent disease outbreaks and epidemics. ■

PHARMACOLOGY WATCH

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

Another Study Implicates Avandia

In this issue: *Rosiglitazone (Avandia) implicated in yet another study; Prilosec and Nexium not associated with cardiac events; Anastrozole (Arimidex) shown more effective than tamoxifen for treatment of early-stage breast cancer; antibiotics show no effect on sinusitis; FDA actions.*

THE HANDWRITING MAY BE ON THE WALL FOR GlaxoSmithKline's rosiglitazone (Avandia) with yet another study implicating the drug with an increased risk of heart failure, cardiovascular events and mortality when compared to other oral hypoglycemic agents. The study was a nested case-control analysis of a retrospective cohort study using health care databases in Ontario. The patient population was nearly 160,000 older (>65 years of age) type 2 diabetics on at least one oral agent. The primary outcome was emergency visit or hospitalization for congestive heart failure, while secondary outcomes were AMI and all-cause mortality. After a mean follow-up of 3.8 years, monotherapy with rosiglitazone was associated with an increased risk of CHF (RR 1.60; 95% CI 2.10; *P*<.001), AMI (RR 1.40; 95% CI, 1.05-1.86; *P*=.02), and death (RR 1.29; 95% CI, 1.02-1.62; *P*=.03). Thiazolidinediones in general were evaluated in the study, but the adverse effects were limited to rosiglitazone. Adverse effects were found in patients who took the drug as a single agent or in combination with other hypoglycemic drugs (*JAMA*. 2007;298:2634-2643). Meanwhile, two large pharmacy benefit managers, Prime Therapeutics and HealthTrans, have dropped rosiglitzone from their formularies and the Department of Veterans Affairs is severely limiting the drug's use. Sales of the drug dropped 27% in the second quarter of 2007 and 39% in the third quarter.

Prilosec and Nexium Cleared

Omeprazole (Prilosec) and esomeprazole (Nexium) are not associated with increased rates of cardiac events, according to statements on the FDA web site. Concern was raised after AstraZeneca submitted data from two long-term studies in patients with severe gastroesophageal reflux to assess treatment with either drug vs surgery. Evaluation of secondary outcomes raised the question of whether long-term use of these drugs increased risk of cardiovascular events including sudden death. In a statement published on the FDA web site (www.fda.gov) on December 10, the agency states that it has completed a comprehensive scientific review of known safety data for both drugs. Based on review of the two studies presented by AstraZeneca and analysis of 14 comparative studies of omeprazole, no evidence of increased rate of cardiac events was seen. "Therefore, FDA continues to conclude that long-term use of these drugs is not likely to be associated with an increased risk of heart problems. The FDA recommends that health-care providers continue to prescribe, and patient's continue to use, these products as described in the labeling for the two drugs."

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Anastrozole over Tamoxifen for Breast Cancer

Anastrozole (Arimidex) is more effective than tamoxifen as adjuvant treatment for early-stage breast cancer according to a study published online as an early release in the *Lancet Oncology*. The study looked at 6241 women with locally invasive breast cancer who were randomized to anastrozole or tamoxifen and followed for a median of 100 months. Primary endpoints were disease-free survival, and secondary endpoints were time to recurrence, incidence of new contralateral breast cancer, time to distant recurrence, overall survival, and death after recurrence. Endpoints were evaluated in the total population and in the hormone-receptor-positive subpopulation. The primary endpoint and all secondary endpoints favored anastrozole except for deaths after recurrence and overall survival for which there is no significant difference. Fracture rates were higher in patients receiving anastrozole compared to tamoxifen. There was no difference in cardiovascular morbidity or mortality between the two treatment groups. The authors conclude that the study "establishes long-term efficacy of anastrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with hormone sensitive, early breast cancer, and provide statistically significant evidence of a larger carryover effect after five years of adjuvant treatment with anastrozole." (*Lancet Oncology* early online publication, 50 December 2007).

Antibiotics and Steroids Not for Sinusitis

Antibiotics and topical nasal steroids are of no benefit for patients with acute maxillary sinusitis according to a new randomized controlled trial of 240 adults. Patients with acute non-recurrent sinusitis were randomized to treatment with antibiotics and nasal steroids, placebo antibiotic and nasal steroid, antibiotic and placebo nasal steroids, or placebo antibiotic and placebo nasal steroid. Amoxicillin 500 mg three times a day for seven days and budesonide spray once daily were the active drug use in the study. The main outcome was proportion of clinically cured at 10 days and the duration of symptoms. Antibiotics made no difference in the proportion of patients with symptoms lasting 10 days or more (29% with antibiotics, 33.6% with no antibiotics). Use of nasal steroid also made no difference for the same measure (31.4% with budesonide, 31.4% with no budesonide). The authors conclude that neither an antibiotic nor topical steroid alone or in combination was effective as the treatment for acute sinusitis in the primary care setting (*JAMA*. 2007;298:2487-2496).

FDA Actions

An expert advisory panel of the FDA has recommended against approving Merck's petition to take lovastatin (Mevacor) over-the-counter. This was the third request in 7 years for OTC status for the cholesterol-lowering drug. The advisers voted 10-2 against approval citing concerns whether patients were capable of determining if they are appropriate candidates for the medication. The FDA generally follows the advice of its advisory panels.

The FDA has approved yet another beta-blocker for the treatment of hypertension. MylanBertek's nebivolol (Bystolic) is a selective beta-1-adrenoreceptor blocker with vasodilating effects. The drug is the 19th beta-blocker approved in the United States.

Wyeth has received an approvable letter for bazedoxifene, a new selective estrogen receptor modulator (SERM) for the prevention of osteoporosis in postmenopausal women. In issuing the letter, the agency asked for more data on the risk of blood clots and stroke, problems that have plagued the other marketed SERM for this indication (raloxifene-Evista). The agency did not ask for new studies however. Wyeth is also seeking the indication for treatment of osteoporosis in postmenopausal women. When approved, bazedoxifene will be marketed as Viviant.

The FDA has issued a safety warning on fentanyl skin patches after several reports of deaths and life-threatening side effects associated with inappropriate use. The warning stresses that the patches are only for patients who are opioid-tolerant and have poorly controlled pain on other narcotic pain medications. The patches are not for postoperative pain or sudden or occasional pain. Patients who used the patch should be aware of the signs of fentanyl overdose. Patients and physicians should be aware of potential drug interactions and physicians and pharmacists need to instruct patients on appropriate use of the patch. Patients also need to be aware that heat sources such as heating pads, electric blankets, saunas, heated waterbeds, hot baths, sunbathing and even fever may result in sudden increases in blood levels of fentanyl.

The FDA has approved a new volume expander for the treatment of volume loss during surgery. German drugmaker Fresenius Kabi's Voluven utilizes a new synthetic starch that is insoluble in water. In clinical trials the product was found to be as safe and effective as Hespan, a currently approved starch solution volume expander. ■