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New Malaria Recommendations for Greece — October, 2011

ABSTRACT AND COMMENTARY

By Mary-Louise Scully, MD

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

Synopsis: *Due to ongoing evidence for malaria transmission in the Laconia (Lakonia) district of Greece, the U.S. Centers for Disease Control and Prevention (CDC) is now recommending that travelers to this area take antimalarial chemoprophylaxis. The enhanced use of personal protection measures against mosquito bites in this and other agricultural areas of Greece is also recommended.*

Sources: CDC Alert. New Malaria Recommendations for Greece. Available at: www.cdc.gov/malaria/malariagreece.htm. Accessed Nov. 5, 2011.

Danis K, et al. Autochthonous *Plasmodium vivax* malaria in Greece, 2011. *Euro Surveill* 2011;6(42). Available at: www.eurosurveillance.org/ViewArticle.aspx?Articleld=19993. Accessed Nov. 5, 2011.

GREEK HEALTH AUTHORITIES RECENTLY PUBLISHED THEIR FINDINGS OF 36 CASES OF *Plasmodium vivax* malaria in Greece occurring between May 2011 and September 2011.[1] Twenty of these malaria cases had no travel history outside of Greece and the remaining 16 cases were in persons from malaria-endemic countries where local transmission vs. importation could not be determined (migrant cases). The majority of all the cases occurred in the southern agricultural area of Evrotas, Laconia. Other areas included the Evia/Euboea (island east of Central Greece), Eastern Attiki, Viotia, and Larissa districts. All 36 cases were confirmed as *P. vivax* by both PCR and microscopy identification.

The median age of reported cases was 36 years, but the median age in migrant cases was lower (24 years) and migrant cases were all male. All cases were hospitalized, treated, and recovered except for one fatality in a patient with underlying cardiac and pulmonary disease who developed acute respiratory distress syndrome. Most patients were treated with a 3-day course of chloroquine followed by a 14-day course of primaquine. Only one case had glucose-6-phosphate dehydrogenase (G6PD) deficiency and, therefore, did not receive primaquine.

The Laconia (Lakonia) district is an agricultural plain that lies in the delta region of the Evrotas River. The authors note that this area has freshwater springs, irrigation and drainage channels, and coastal wetlands that provide ideal breeding grounds for the 15 species of *Anopheles* mosquitoes found in Greece, of which five species are considered to be potential malaria vectors. *Anopheles sacharovi* and *Anopheles claviger* were the most commonly identified species in the areas of outbreaks.

In the Evrotas area, it is estimated that migrant farm workers make up 2,000-4,000 of the total population of 4,485 depending on the time of year. Approximately 80% of migrant workers in this area are from Pakistan, about 15% from Romania, and the remaining are from Morocco. In the other outbreak areas of Greece there were also high numbers of migrant workers from malaria-endemic countries, especially the Indian subcontinent. These areas of Greece are not typically visited by tourists.

In light of the ongoing evidence of malaria transmission in the Laconia district of Greece, the U.S. CDC now recommends that travelers to this destination take malaria chemoprophylaxis. Appropriate anti-malarials (U.S. CDC) include atovaquone-proguanil (Malarone®), chloroquine, doxycycline, mefloquine, or primaquine. Use of primaquine requires prior testing for G6PD deficiency.

■ COMMENTARY

Malaria was eradicated from Greece in 1974, though occasional sporadic cases of local mosquito-borne transmission have occurred throughout the years. This outbreak is unique both in the number of cases and the sustained transmission that is ongoing. The combination of ideal climate, close proximity of human and mosquito populations, and increasing numbers of migrant workers from malaria-endemic countries are contributing to the outbreak.

All the cases were secondary to *P. vivax*, for which full treatment requires presumptive anti-relapse therapy (PART) with primaquine to eradicate the hypnozoite forms that remain dormant in the liver. The dose is 30 mg/day for 14 days. Primaquine is contraindicated in persons with G6PD deficiency and pregnant females, so testing is necessary before its use. The most prevalent G6PD variants are G6PD A- and G6PD Mediterranean. These variants can result in severe hemolysis by the sudden destruction of older, more enzyme-deficient red blood cells after exposure to drugs like primaquine, nitrofurantoin, sulfamethoxasole, or foods such as fava beans.[2]

In addition to the recommended use of anti-malarials in travelers to the Laconia district of Greece, clinicians globally should to be aware of this outbreak and include malaria in the possible differential diagnosis of any febrile patient returning after travel to Greece. ■

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Good Riddance to Rinderpest: Human Implications

ABSTRACT AND COMMENTARY

By Maria D. Mileno, MD

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

Synopsis: *A declaration made on May 25, 2011, by a number of authorities states that the veterinary disease, rinderpest, has been eradicated. While the rinderpest virus does not cause human disease, it is in the Morbillivirus family, which contains important pathogens of humans and animals, such as measles. This perspective, published in the* Journal of Infectious Diseases*, gives us insights into the devastation rinderpest once caused, and expresses hope that measles may also soon be eradicated.*

Source: Morens DM, et al. Global rinderpest eradication: Lessons learned and why humans should celebrate too. *J Infect Dis* 2011;204:502-505.

Since the time of the Roman Empire the animal virus, rinderpest (RPV), German for "cattle plague," has led to countless human deaths from agricultural losses that resulted in famine and disease. The Great Ethiopian Famine of 1887-1892 is attributed to a rinderpest panzootic disease, and caused loss of virtually all cattle, buffaloes, and wild swine as well as many sheep, goats, and wildlife.[1,2] Fertile Ethiopian lands became a graveyard without cattle to plow fields and no animal dung to fertilize crops. The disruption of this intricate balance of nature led to a surge of crop-destroying rats and swarms of locusts and caterpillars, resulting in famine and devastation in proportion to that of a biblical plague. Not just responsible for decimation of African species, RPV also affected European bison. Brief importation to the United States in the 1860s was recorded, although disease was not established.[3]

The virus is a single-stranded RNA virus of the family Paramyxoviridae. Transmission typically occurs via inhalation during close contact with an infected animal with viral-containing nasal oral or fecal secretions. There is a silent incubation period for 8-11 days with prolonged fever and a violent diarrheal stage of 1-2 days causing dehydration and death or gradual recovery. Documented mortality rates often approach 100%, although milder disease, resulting from infections from stable strains with reduced virulence, is associated with lower mortality rates of 5%-10%.

Phylogenic analysis shows that RPV is the closest relative of measles virus. This strongly suggests that RPV or a similar virus gave rise to measles. It is probable that an ancestral RPV-like virus jumped to humans when we began to domesticate cattle for agricultural purposes and the virus evolved into the current infectious agent of the measles virus.

■ COMMENTARY

Rinderpest was the first infectious disease to be successfully controlled by active intervention. We can attribute many aspects of infectious disease control practices to rinderpest. The techniques for restriction of animal movement, isolation, animal destruction, and disinfection were later applied to human diseases and became cornerstones of public health practice. Rinderpest led to one of the earliest conceptions of infectious diseases and one of the first plans to vaccinate against an infectious disease — 9 years before the 1720 European introduction of smallpox inoculation.[4] The first demonstration of protective maternal immunity and even one of the first uses of a thermometer to document febrile illness are linked to rinderpest. Long associated with war and natural disasters, RPV was one of the first infectious agents to be considered as a potential bioweapon. The ravages of this virus led directly to the establishment of the Office International des Epizooties (OIE) in 1924.

There is no evidence that RPV infects humans symptomatically. That it is so closely related to measles virus may be a boon. A new and somewhat ironic step in disease control of measles might well be this eradication of RPV: Eradicating the ancestor of measles may be accomplished before the eradication of measles itself.[5] Measles and RPV share critical features that lend themselves to eradication:

- A single viral immunotype
- Few unapparent infections
- Lack of chronic carrier states
- Vaccine induction of long-standing protective immunity

Also, measles virus has no extrahuman reservoir. Hence, there would be no hidden pockets of viral propagation to contend with. Rinderpest has had a profound influence on the field of infectious diseases and public health. So too will its eradication. ■

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Pre-transplant Serologies in a Man from West Africa

CASE REPORT

By Neha Nanda, MD

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

A 40-YEAR-OLD GAMBIAN MALE WITH END-STAGE RENAL disease secondary to focal segmental glomerulosclerosis (FSGS) was evaluated for a living unrelated kidney transplant. He had received immunosuppressive therapy for FSGS in the past, including long-term cyclosporine, prednisone, and recently, CellCept® (mycophenolate), with a poor therapeutic response, and was transitioned to hemodialysis 1 year prior to evaluation. He entered the United States 10 years ago, and made frequent trips to Gambia and the Ivory Coast to visit family. His last visit to Gambia was 16 months ago, and lasted for 1 month.

Prior to travel he was seen at a travel medicine clinic where he had received malaria prophylaxis and pre-travel vaccinations. On returning to the United States, he did not report any new constitutional symptoms. In preparation for an elective kidney transplant, serological tests for schistosomiasis, filariasis, and strongyloidiasis were obtained. Anti-schistosoma IgG and anti-filaria IgG4 antibody levels were elevated, and an anti-strongyloides IgG antibody level was high normal. His review of symptoms, including fevers, rashes, hematuria, increasing swelling in his lower extremities, and shortness of breath, was negative. The unrelated kidney donor was from the United States. The patient's physical examination was unremarkable except for a patent arterial-venous fistula in his left arm. White blood cell count was 6,000 cells/µL with a persistent mild eosinophilia varying from 8% to 12%. Anti-schistosoma IgG serology was positive at 0.6 optical density (OD; normal, 0-0.1). This was consistent with untreated active infection, or infection acquired in the past. Anti-filarial IgG4 was elevated at 0.9 (normal, < 0.8) and reported as "equivocal." Anti-strongyloides IgG was "high negative" at 1.47 (normal, < 1.49). A positive anti-strongyloides IgG antibody indicates current active, latent, or resolved previous infection. Multiple stool samples evaluated for ova and parasites were negative. Peripheral blood smears were unremarkable; specifically, no microfilaria were observed. Urinalysis did not show hematuria. Serological tests for HTLV-1 and HIV infections were negative.

How should one approach a potential renal transplant candidate who presents with such serological data? Could he still be at risk from these infections after his departure from an endemic setting? Will immunosuppressive agents potentially increase the morbidity associated with these infections?

Individuals traveling to West Africa are at risk of acquiring many classical tropical infections including malaria, dengue fever, schistosomiasis, filariasis, and strongyloidiasis. When evaluating individuals before solid organ transplantation, it is prudent to identify such infections and treat accordingly. After transplantation, patients receive potent immunosuppressive agents to prevent rejection. A latent infection may progress to an active, even fulminant, form of disease. Parasites posing the greatest risk can multiply within the host months or years after the patient has left an endemic area, if the pathogen can continue its life cycle by autoinfection or remain latent in the human host.

Schistosoma mansoni, *S. haematobium*, and *S. intercalatum* are endemic to West Africa. Schistosomiasis can manifest itself as an acute infection (Katayama fever syndrome) or as a chronic infection. Individuals being considered for transplantation should be evaluated for chronic schistosomiasis if they have an appropriate exposure history. In chronic schistosomiasis, adult worms can remain viable for years in the circulation surrounding the intestines, urinary bladder, or liver. The inflammatory response to ova normally results in granuloma formation within these organs. Symptomatic hepatic and gastric schistosomiasis have been reported in liver transplant recipients.[1] The recipients had positive anti-schistosoma serology before transplant and ova were found in gastric and liver biopsies in the post-transplant period. Both these cases were potentially a result of accelerated ova production. The actual effects of immunosuppression on ova production or migration of adult worms are unknown. Although reactivation of schistosomiasis has not been reported in renal transplant recipients, they tend to have more urological complications in the post-transplant period. Therefore prior to transplant, obtaining serology for schistosomiasis in addition to stool and urine for ova is recommended. If the potential recipient does have a

positive serology or has ova in the stool/urine sample, treatment with praziquantel should be initiated in the pre-transplant period.

Wucheria bancrofti is one common species implicated in filariasis. Inhabitants of West Africa may demonstrate either asymptomatic microfilaremia or symptomatic infection, i.e., lymphedema or tropical pulmonary eosinophilia. The adult worms can survive in the human lymphatic system or subcutaneous tissue for years, producing microfilariae that travel in the circulation to reach lungs, heart, or kidneys. Adult worms can live in the human body for up to 7 years.[2] Filariasis can reactivate during the post-transplant period, and has been reported to cause graft dysfunction and lymphocele following renal transplantation.[3] To prevent such complications, filarial antibody studies and peripheral blood smears for microfilariae should be obtained prior to a transplant if prior exposures have occurred. If either test is positive, the patient should receive appropriate treatment. Diethylcarbamazine citrate (DEC) is the drug of choice and can be obtained from the Centers for Disease Control and Prevention. Other effective regimens are combinations of ivermectin, albendazole, and doxycycline. Doxycycline causes sterility in the adult female worms.[4]

Strongyloides stercoralis is unique in its ability to perpetuate human infections by autoinfection. After transplantation it can cause a severe hyperinfection syndrome since the autoinfection cycle is up-regulated in the face of immunosuppression.[2] Potential transplant recipients who have appropriate exposures should be evaluated for active infections. Stool samples should be examined for larvae and strongyloides serology (IgG) should be obtained, especially if there is unexplained eosinophilia. If either is positive, treatment with ivermectin should be initiated.

Since our patient was a renal transplant candidate, we treated him for presumptive schistosomiasis, filariasis, and strongyloidiasis on the basis of his serological findings. He received praziquantel for schistosomiasis and ivermectin for strongyloidiasis. For filariasis he received albendazole, doxycycline, and additional ivermectin. After treatment, his white blood cell count was 5,400 cells/µL and eosinophilia had resolved. He successfully underwent a living unrelated kidney transplant 1 week after therapy. After transplantation he was started on routine immunosuppressive regimen with excellent postoperative recovery. At the 2-month follow-up to his renal transplant, he was doing well. ■

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Dengue Outbreak in Kenya: Sign of a Larger Issue?

OUTBREAK AND UPDATE

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

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

Synopsis: *An outbreak of dengue fever in northeastern Kenya has recently sickened at least 5,000 people.*

Source: ProMed Archive Number 20111004.2985; Oct. 4, 2011.

AN OUTBREAK OF DENGUE FEVER IN NORTHEASTERN KENYA was first reported in September 2011, and is believed to be spreading rapidly, with at least 5,000 people infected within the first weeks of this outbreak. The Kenyan Ministry of Public Health reported 4 confirmed deaths, but with only one public hospital and a few private clinics in the epicenter (Mandera, near the border with Ethiopia and Somalia), the toll was likely higher.

Another recent, large epidemic of dengue occurred on the Cape Verde Islands off the West African coast in March 2010, with more than 21,000 suspected cases and 6 deaths reported by the U.S. Centers for Disease Control and Prevention; almost 60 cases were also reported by ProMed in nearby Senegal. Unfortunately, poor diagnostic capabilities in these West African countries likely adversely affected the accuracy of the surveillance data obtained during that outbreak.

■ COMMENTARY

Dengue fever, an arboviral disease with a typical incubation period of 4-7 days, is caused by four circulating serotypes of dengue virus. This disease is not usually considered a major threat to travelers to Africa. Although

this outbreak in remote northeastern Kenya did not occur near areas frequented by tourists, dengue fever does pose a threat to travelers and relief works in Africa. Of 24,920 returned travelers seen at GeoSentinal clinics from March 1997 to March 2006, 28% cited fever as a chief reason for seeking care. Dengue was the cause of fever for 6%, although this diagnosis was made less frequently than malaria (21% of febrile travelers) and diarrheal illness (15% of febrile travelers).[1] Although dengue was diagnosed in only 1% of the febrile travelers who had been to sub-Saharan Africa in this study, the poor surveillance for dengue in the region undoubtedly contributed to the low reported numbers. In a large review of ill returned travelers, dengue fever was primarily found in travelers returning from southeast Asia (especially in June and September), south Central Asia (especially in October), South America (especially in March), and the Caribbean (especially in August and October).[2] One study estimated the incidence of dengue fever to be nearly 3% in Dutch travelers who spent a median of 1 month traveling in Asia (where travel-related dengue is a more frequent diagnosis) in the early 1990s.[3]

A 1956 retrospective serosurvey suggested that dengue has existed in Africa at least as far back as 1926-1927, when it caused a major epidemic in Durban, South Africa. Despite poor surveillance for dengue in most of Africa, it is clear that fever caused by all four serotypes has increased dramatically since 1980, as multiple outbreaks of dengue have occurred in most regions of Africa over the past three decades.[4] Table 1 *(below)* reveals past epidemics of dengue and serotypes that have been documented in Africa. It has been presumed that these outbreaks have most likely been transmitted by *Aedes aegypti*, which is widely distributed in the region.

Because most dengue infections are subclinical or manifest as undifferentiated fever, they are often undiagnosed or are treated as malaria or other febrile illnesses endemic to a given area, such as typhoid or leptospirosis. Chikungunya is another viral infection that mimics dengue and also circulates in sub-Saharan Africa. Given the recently documented outbreaks of dengue in sub-Saharan Africa, this infection may be more of an issue there than currently appreciated, and the relatively low case numbers a product more of poor surveillance rather than low disease burden. Thus, dengue should not be discounted as a possible cause of fever in travelers returning from Africa, and hopefully epidemiological studies will better define the distribution of dengue in Africa in the coming years.[5] ■

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Table 1. Time line of dengue epidemics, classified by country of outbreak and serotype.

Epidemic/detection	Country	Serotype	Reference
Past epidemics and reported cases of dengue in East Africa			
1977-1979	Seychelles	DEN-2	Metselaar et al (1980)
1982	Kenya	DEN-2	Johnson et al (1982)
1984-1985	Mozambique	DEN-3	Gubler et al (1986)
1985-1986	Sudan	DEN-1, DEN-2	Hyams et al (1986)
1991-1992	Djibouti	DEN-2	Rodier et al (1996)
1992-1993	Somalia	DEN-2, DEN-3	Kanesa-Thesan et al (1994), Sharp et al (1995)
1948, 1984, 1993	Comoros	DEN-1, DEN-2	Boisier et al (1994)
2005	Eritrea	Not determined	Unpublished
Past epidemics and reported cases of dengue in West Africa			
1964-1968	Nigeria	DEN-1, DEN-2	Carey et al (1971)
1974-1985	Senegal	DEN-2	Saluzzo et al (1986)
1983-1986	Burkina Faso	DEN-2	Robert et al (1993), Herbey et al (1984)
1982	Burkina Faso	DEN-2	Gonzalez (1985)
1980, 1990	Senegal	DEN-2, DEN-4	Saluzzo et al (1986), Traore-Laminaza (1994)
1999-2000	Senegal	DEN-2	Diallo et al (2003)

Adapted from: Sang R. Dengue in Africa. Available at: www.tropika.net/review/061001-Dengue_in_Africa/article.pdf. Accessed Nov. 6, 2011.

able dengue virus infection amongst Dutch travellers to Asia. *Trop Med Int Health* 2002;7:331-338.
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Pediatric VFRs, Preemies, Adoptees, and Mountaineers

ABSTRACT AND COMMENTARY

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Synopsis: *Recent publications suggest that children traveling to visit friends and relatives are at relatively high risk of increased exposure to infections, that former premature babies without persisting lung disease are safe at oxygen levels of commercial aircraft, that a single screening stool parasite exam might not be adequately sensitive in foreign-born adoptees, and that a child's past experience with altitude sickness is not necessarily predictive of future responses to altitude.*

Source: Valerio L, et al. Epidemiologic and biogeographic analysis of 542 VFR traveling children in Catalonia (Spain). A rising new population with specific needs. *J Travel Med* 2011;18:304-309.

Approximately 2 million children cross international borders each year, and many of them are traveling with older family members to visit friends and relatives (VFR) in the family's country of origin. Previous studies suggest that these children are at particular risk of missing potentially helpful pre-travel interventions and of becoming ill during travel. Now, investigators in Spain have compared demographic features of 542 pediatric VFR travelers and 156 tourist travelers younger than age 15 years.

The VFR travelers were younger and came for pre-travel care closer to the time of departure (22 vs. 32 days) than tourist travelers. They were more likely to stay in private homes and to visit rural areas during their trips. They also stayed overseas longer (52 vs. 17 days).

These data help identify reasons why VFR traveling children might be at greater risk of becoming infected and ill during their trips. It is not because they are "bad" or do something "wrong." Rather, it is because they are younger and have more prolonged exposures to infection vectors than do typical tourist travelers. All children traveling to developing countries should benefit from pre-travel care. We should especially focus our preventive efforts on younger travelers and on travelers embarking on long trips — whether they are visiting friends and relatives or not.

Source: Bossley CJ, et al. Fitness to fly testing in term and expreterm babies without bronchopulmonary dysplasia. *Arch Dis Child Fetal Neonatal Ed* 2011 Sept 13; Epub ahead of print: doi:10.1136/adc.2011.212001.

Commercial aircraft are pressurized to yield an environment similar to that containing 15% oxygen. Former premature infants with chronic lung disease (bronchopulmonary dysplasia) often need oxygen supplementation with air travel, but data were limited for former premature infants without lung disease. Forty-one term babies and 30 former premature babies without chronic lung disease were exposed to 15% oxygen for 20 minutes at 3 and 6 months corrected gestational age. Oxygen saturations dropped a median of 6%, and relative hypoxia was not different based on either gestational age or age at testing. Only 5% of term and 7% of pre-term (not statistically different) infants developed hypoxia (oxygen saturation < 90% for more than 2 minutes). Transient desaturations (an additional 4%-6%) occurred with feeding.

Significant desaturations are not likely in former premature infants during exposure to aircraft-like environments. Routine fitness-to-fly testing is not warranted in these babies unless they have known lung disease. At the same time, however, potential consequences of mild oxygen desaturations have not been fully studied.

Source: Staat MA, et al. Intestinal parasite screening in internationally adopted children: Importance of multiple stool specimens. *Pediatrics* 2011 Aug 8; Epub ahead of print.

Travel medicine practitioners are often involved in the care of families traveling overseas to adopt children. Returning "home," the adoptees are screened for potentially contagious, but perhaps asymptomatic, intestinal parasite infections. Standards of care have changed from an automatic screening of three stools on separate days to less extensive testing. Is that appropriate?

The authors evaluated 1,042 internationally adopted children who had undergone stool testing. Of these, 27% had a parasite identified. (Some were *Blastocystis hominis*, a parasite of limited pathogenicity. *Giardia* was most common and could have been identified by antigen testing rather than microscopic exam.) Parasites were more likely to be found in children from Ethiopia (55%) and Ukraine (74%) than in children from China (13%), Gua-

temala (9%), or Korea (0%). Of those with at least one positive result, a single stool was positive in 79%, and two separate stools found parasites in 92%.

These data give us a good clue about areas of risk for intestinal parasites (Ukraine and Ethiopia), and they point to the ongoing value of repeated stool samples to find parasitized children. The authors suggest altering current practice standards so as to routinely test multiple stool samples for recently arrived international adoptees.

Source: Rexhaj E, et al. Reproducibility of acute mountain sickness in children and adults: A prospective study. *Pediatrics* 2011;127:e1445-1448.

MANY TRAVEL MEDICINE PRACTITIONERS USE A TRAVELER'S previous experience at altitude to determine whether to provide acetazolamide for individuals going to high altitudes. Is it wise to withhold preventive treatment from a child going to altitude just because a previous similar trip was not associated with acute mountain sickness?

Swiss and Chilean investigators prospectively evaluated 27 children and 29 adults who resided at low altitudes during two separate trips to 3,450 meters elevation. On the first ascent, 62% of adults and 22% of children had mountain sickness, with 48% of adults and 15% of children becoming symptomatic on the second trip. No child had acute mountain sickness on both trips, but no adult without symptoms on the first trip developed symptoms on the second trip.

These data are novel in showing that acute mountain sickness might indeed be less common in children than in adults; previous experience and research had suggested otherwise. Interestingly, however, lack of mountain sickness on one trip does not imply that the child will be symptom-free on a subsequent trip nor does one symptomatic trip imply that a child is at significant risk of another. One could advocate for acetazolamide use in adults based on seemingly higher risk and repeatability of symptoms, but children are at lower and less predictable risk than their adult companions. ■

CME Objectives / Instructions

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

- discuss the latest data regarding the diagnosis and treatment of various travel-related diseases;
- explain new data concerning recommended precautions and prophylaxis for patients traveling to specific areas of the world;
- implement strategies in the practice setting to inform patients of disease outbreaks and epidemics relevant to their travel plans.

To earn credit for this activity, please follow these instructions.

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME Questions

1. **Which of the following statements about recent autochthonous malaria cases in Greece is *true*?**
   a. Recent malaria cases in Greek migrant workers had high mortality rates.
   b. Primaquine should not be used for prophylaxis in travelers to Greece especially among expatriates.
   c. G6PD Mediterranean variants are at risk of severe hemolysis with primaquine administration.
   d. Malaria cases were in Greece were secondary to both *P. falciparum* and *P. vivax*.

2. **Rinderpest infections are:**
   a. asymptomatic or mild in humans.
   b. directly related to subsequent rubella outbreaks among humans.
   c. confined to forested jungle areas in the Rift Valley basin.
   d. vaccine-preventable.
   e. currently endemic in sub-Saharan Africa.

3. **A 35-year-old male from Puerto Rico is undergoing pre-transplant evaluation prior to liver transplantation. His physician orders a strongyloides IgG antibody test, which returns positive. Several stool samples have been tested for strongyloides larvae and are negative. What should be done next?**
   a. Disregard the serology results as there are no larvae in stool.
   b. Repeat strongyloides blood serology in 3 months.
   c. Treat with ivermectin 200 µg/kg/day for 2 days.
   d. Proceed with transplantation, but treat with ivermectin if he becomes symptomatic in the post-transplant period.

PHARMACOLOGY WATCH

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

HPV Vaccine Now Recommended for Males

In this issue: New recommendations for HPV vaccine; guidelines for treatment of essential tremor; updates on smoking cessation drugs; and FDA actions.

HPV vaccine and anal cancer risk

The human papillomavirus (HPV) vaccine is routinely administered to adolescent girls; now the CDC's Advisory Committee on Immunization Practices is recommending the vaccine for 11- and 12-year-old boys as well. The vaccine has been approved for use in both adolescent girls and boys to protect them against HPV but has been somewhat underutilized in girls and rarely used in boys. HPV causes genital warts and cervical cancer in women and the vaccine effectively reduces the rate of both. The vaccine is generally recommended for 11 and 12 year olds when they get other routine vaccines, and before they become sexually active. Although the vaccine is approved for boys, the CDC had not made a recommendation on routine use until now. After evaluating data on efficacy in males, the committee felt that the vaccine could protect boys against genital warts, as well as throat and anal cancer caused by HPV, and could help prevent spread of the virus to girls.

In related news, a new study shows the HPV vaccine is effective in preventing anal intraepithelial neoplasia in men who have sex with men. In a double-blind study of 602 men (ages 16-26) who have sex with men, half were randomized to the quadravalent HPV vaccine and half to placebo. The vaccine reduced the risk of anal intraepithelial neoplasia caused by the four subgroups of HPV covered by the vaccine (HPV-6, 11, 16, and 18) by half in the intention-to-treat population and by 77% in the per-protocol population. Anal intraepithelial neoplasia caused by HPV of any type was reduced by 25.7% and 54.9%, respectively. Rates of anal intraepithelial neoplasia per 100 person years were 17.5 in the placebo group and 13 in the vaccine group in the intention-to-treat, and 8.9% placebo vs 4.0% vaccine in the per-protocol population. The rate of grade 2 or 3 anal intraepithelial neoplasia related to HPV subtypes covered by the vaccine was reduced by 54.2% (intention-to-treat) and 74.9% (per-protocol). The vaccine was well tolerated. The authors conclude that the HPV vaccine reduced the rate of anal intraepithelial neoplasia in men who have sex with men and may help reduce the risk of anal cancer (*N Engl J Med* 2011;365:1576-1585). ■

Treatment of essential tremor

The American Academy of Neurology has published its updated guideline for the treatment of essential tremor. Propranolol and primidone remain first options with a Level A recommendation (established as effective). Alprazolam, atenolol, gabapentin as monotherapy, sotalol, and topiramate are graded as Level B (probably effective), while nadolol, nimodipine, clonazepam, botulinum toxin a, deep brain stimulation, and thalamotomy remain as level C (possibly effective). There is not enough evidence to make a recommendation for gamma knife therapy. The new guideline also states that there is insufficient evidence to support or refute the use of pregabalin, zonisamide, or clozipine. Levetiracetam and 3,4 diaminopyridine are ineffective and flunari-

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zine is probably ineffective. The guideline was published online in *Neurology* October 19, 2011 (doi: 10.1212/WNL.0b013e318236f0fd). ■

Chantix and neuropsychiatric side effects

There is good news for the smoking cessation drug varenicline (Chantix). Following concern about neuropsychiatric side effects, the FDA sponsored two epidemiologic studies that evaluated the risk of neuropsychiatric hospitalizations associated with the drug. Neither study found a difference in risk of neuropsychiatric hospitalization between varenicline and nicotine replacement therapy, although hospitalization was the only endpoint evaluated and they did not rule out an increased risk of other neuropsychiatric events. While reassuring, the FDA is recommending that health care professionals and patients continue to follow the recommendations previously established and monitor for neuropsychiatric symptoms when prescribing or using varenicline. The manufacturer is conducting a large safety study of the drug to assess neuropsychiatric adverse effects but the results will not be available until 2017 (www.fda.gov/Drugs/DrugSafety/). In related news, the inexpensive partial nicotine agonist cytisine is an effective adjunct to smoking cessation, according to a new study in the *New England Journal of Medicine*. Cytisine is extracted from the seeds of *Cysisus laborinum L.* (Golden Rain acacia) and has been available worldwide for years, particularly in Eastern Europe, where it can be purchased for $6-$15 per course. Researchers randomized 740 smokers to cytisine or matching placebo for 25 days along with counseling. The rate of sustained 12 months abstinence was 8.4% in the cytisine group compared with 2.4% in the placebo group ($P = 0.01$). GI side effects were slightly more prevalent in the treatment group. The authors conclude that cytisine was more effective than placebo for smoking cessation and may be "an affordable treatment to advance smoking cessation globally" (*N Engl J Med* 2011;365:1193-1200). ■

FDA Actions

The FDA is continuing to review the association of oral contraceptives and thrombotic risk, particularly oral contraceptives containing drospirenone. On October 27, the FDA issued a preliminary Drug Safety Communication, with the full report due out in early December. Reviewing the records of Kaiser Permanente members in California and state Medicaid programs in Tennessee and Washington, which included 835,826 women receiving contraceptive prescriptions from 2001-2007, an increased risk of venous thromboembolism (VTE), deep venous thrombosis, and pulmonary embolism was noted with several contraceptives, with low estrogen hormonal contraceptives as a reference. Products containing drospirenone had relative risk of VTE of 1.74 (95% confidence interval [CI] 1.42-2.14). The norelgestromin/ethinyl estradiol transdermal patch was associated with relative risk of 1.55 (95% CI 1.17-2.07) and etonogestrel/estradiol vaginal ring was associated with a relative risk of 1.56 (95% CI 1.02-2.37). The risk was higher in younger users then older women (www.FDA.gov./DRUGS/DrugSafety/ucm277346.htm).

The FDA has approved the first generic olanzapine (Zyprexa) to treat schizophrenia and bipolar disorder. The generic carries the same warnings as the brand regarding increased risk of death in elderly people with psychosis or dementia. Generic olanzapine will be available from several manufacturers as tablets and orally disintegrating tabs.

The FDA has announced that drotrecogin alfa (Xigris) is being withdrawn from the market by Eli Lilly & Co. The withdrawal is based on the results of the recently completed PROWESS-SHOCK trial in which drotrecogin alfa failed to show a survival benefit in patients with severe sepsis and septic shock. The FDA is recommending that the drug should be stopped in any patients currently being treated and should not be initiated in new patients. All remaining product should be returned to the supplier.

The FDA has approved tadalafil (Cialis) for the treatment of benign prostatic hyperplasia (BPH) either alone or when it occurs along with erectile dysfunction (ED). The drug was approved in 2003 for treatment of ED. The approval was based on two trials in which men taking tadalafil 5 mg daily experienced significant improvements in BPH symptoms compared with those taking placebo. A third study in which men had both BPH and ED, tadalafil 5 mg daily improved both symptoms of BPH and ED compared to placebo. Tadalafil should not be used in patients taking nitrates or in combination with alpha blockers for the treatment of BPH.

The FDA has approved a combination of sitagliptin and simvastatin for the treatment of adults with type 2 diabetes and hypercholesterolemia. This represents the first combination drug for treating these two conditions. The fixed dose combination is available in three strengths: 100 mg sitagliptin/10 mg simvastatin, 100 mg/20 mg, and 100 mg/40 mg. The approval was based on "substantial experience with both sitagliptin and simvastatin" and is a "convenience combination," according to the FDA. Sitagliptin/simvastatin will be marketed as Juvisync by MSD International GmbH Clonmel in Tipperary, Ireland. ■