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INSIDE

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Chemoprophylaxis of Malaria—2000

CONFERENCE UPDATE

By David R. Hill, MD, DTM&H

For the last decade, the chemoprophylaxis of malaria has relied upon only a few medications—chloroquine, proguanil, mefloquine, and doxycycline. With chloroquine resistance continuing to be a problem in most malarious areas of the world, and an ongoing controversy about the safety and tolerance of mefloquine, travel health advisors have been anticipating new drugs to prevent malaria. Much information addressing prophylaxis was presented at the 48th annual meeting of the American Society of Tropical Medicine and Hygiene. Before focusing on medications, however, it is important to discuss compliance with chemoprophylaxis. No medication will work if it is not taken.

Dr. H. Lobel and colleagues from the CDC, Lufthansa Airlines, and the Kenya Medical Research Institute surveyed returning East African travelers for use of antimalarials (*Abstract #511*). Noncompliance was most frequent in younger travelers, those who were overseas more than a month, and those who attributed medical problems to their medications. Decreased compliance has also been documented with medications that are taken daily (such as doxycycline and proguanil) or need to be purchased overseas (such as proguanil for U.S. travelers). And, many travelers will discontinue medication when they return home, rather than continuing it for four weeks. Neuropsychiatric side effects were seen in 1%-13% of mefloquine users, depending upon their country of origin, but infrequently led to discontinuation. The message from this study is the need to emphasize to travelers the importance of compliance (with both chemoprophylaxis and mosquito avoidance), and to help them understand the most likely side effects so they do not discontinue drugs based on misconceptions of risk and side effects.

Weekly chloroquine phosphate (500 mg) plus daily proguanil (200 mg) has been advocated, particularly by the British, for chemoprophylaxis in areas of low transmission of resistant malaria, such as India. Dr. R. Behrens from the London School of Hygiene and Tropical Medicine presented a rationale for continued use of this combination. However, several negatives mitigate against wide acceptance. U.S. travelers must purchase proguanil en route to the malarious area, and in our experience 25% fail to do so, leaving them on a single ineffective drug. The combination, although reasonably well tolerated, does have gastrointestinal (GI) side effects, can cause apthous ulceration in the mouth, and has a protective efficacy of about 70% in resistant areas. Thus, if it is used, the traveler should be

warned about the possibility of breakthrough malaria while on chemoprophylaxis.

Doxycycline remains an important alternative for persons who are intolerant of mefloquine or who travel to areas where there is both chloroquine and mefloquine resistance, such as the rural hill country in the border areas of Thailand with Myanmar. Dr. C. Ohrt of the Walter Reed Army Institute of Research reviewed data published over the last two decades that document the excellent efficacy of doxycycline against both *Plasmodium falciparum* and *P. vivax*. He emphasized that doxycycline cannot be used as a casual prophylactic (i.e., it does not reliably kill parasites that are differentiating and developing in the liver). Therefore, it must be taken for four weeks after leaving the malaria-endemic area. It should also be taken with sufficient liquid or food to ensure complete passage into the stomach because if it remains in the esophagus it can cause erosions. Other well-known side effects include photosensitivity and vaginal yeast infection, and it cannot be used during pregnancy and in children younger than the age of 8 because of teeth staining.

There has been recent interest in another antibiotic, the macrolide azithromycin. It is well tolerated, and is safe in children (available as an oral suspension) and during pregnancy. Because of promising in vitro effects and efficacy as a suppressive agent in challenge studies with sensitive parasites, it was examined in field trials in the late 1990s, usually in a dose of 250 mg/day. Unfortunately, although it demonstrated excellent protection against *P. vivax* (> 95%), and moderate efficacy against *P. falciparum* in semi-immunes in Kenya (83%), it had unacceptably low protection in Thailand (69%) (*Abstract #25*), and in nonimmunes in Indonesia (72%). This has led to azithromycin no longer being developed as a single agent for prevention; it is now being studied in combination with other antimalarials.

Two new and exciting areas are the development and imminent release of Malarone (Glaxo Wellcome), a fixed combination of atovaquone (250 mg) and proguanil (100 mg), and the rebirth of the 8-aminoquinolines as prophylactics. Malarone is already available for treatment of malaria in Canada and in many countries of the European Union. Dr. D. Shanks of the U.S. Army Medical Research Unit in Kenya reviewed the clinical experience with Malarone. When used as a therapeutic agent for multi-drug-resistant *P. falciparum*, it has an excellent efficacy ranging from 95% to 100%. Studies from Kenya, Zambia, and Gabon document its effectiveness as a prophylactic in both children and adults, with efficacy rates of 95% to 100% against *P. falciparum*. Malarone can be discontinued soon after exposure because of its ability to kill exo-erythrocytic organisms of *P. falciparum*. Thus, it is a causal prophylactic for *P. falciparum*. It is generally well tolerated; GI effects are most common, and reversible elevation of liver enzymes can occur when used for treatment (at a dose 4 times that of prophylaxis). It also appears safe in persons with G-6-PD deficiency (*Abstract #424*).

The addition of malarone to drugs available for prevention of malaria is welcome and provides an alternative for persons intolerant of mefloquine and young children who cannot take doxycycline. It can be targeted for those going on short trips who would only need to take chemoprophylaxis for several days, for travel to multidrug-resistant areas, and for those who prefer a daily regimen. It should be started one to two days before travel, taken daily during exposure, and continued for seven days after leaving the malarious area. It will not kill hypnozoites (dormant liver-phase parasites) of *P. vivax* or *P. ovale*, so persons who are at high risk for these species will need to take terminal prophylaxis with primaquine. Concerns raised with malarone's efficacy studies are that they have been carried out in semi-immune persons and that there has been only limited experience in prevention of *P. vivax* and *P. ovale* malaria. However, preliminary information indicates it has a high degree of efficacy in nonimmunes, and information from treatment studies indicates that it should be effective in areas endemic for nonfalciparum species.

A new role for 8-aminoquinolines is in chemoprophylaxis. The best known agent, primaquine, is currently limited to terminal prophylaxis or radical cure of *P. vivax* and *P. ovale* malaria because of its ability to eradicate the hypnozoites of these species. Dr. Baird of the Naval Medical Research Center and Dr. Prescott of the Walter Reed Army Institute of Research discussed these agents. Studies in the last five years have demonstrated that a dose of 30 mg base daily (or equivalent) is effective in protecting against both *P. falciparum* (85%-95% protective efficacy) and *P. vivax* (85%-90%). It can also be used as a causal prophylactic, which allows discontinuation of the drug within a week after leaving the malarious region. With the dose of 30 mg daily, however, tolerance is an issue; about 15% of persons report side effects. Taking the drug with food may decrease the incidence of gastrointestinal upset.

Because primaquine is an oxidant stress it can cause hemolysis in G-6-PD-deficient persons. The mild deficiency variant occurs in about 10% of Africans; there is a rare variant among Caucasians (particularly those of Mediterranean descent) and Asians, which may result in life-threatening hemolysis. Thus, a G-6-PD level needs to be obtained before prescribing the drug. This also precludes its use in pregnant women in whom the G-6-PD status of the unborn child cannot be determined. Methe-

moglobinemia is another concern, and increases in severity with longer use of the drug. Thus, primaquine has good potential as a causal prophylactic in persons on short-term trips who have normal G-6-PD levels. This indication, however, needs to be submitted to the FDA for review.

Another promising 8-aminoquinoline is tafenoquine (WR 238605). It has excellent efficacy in achieving radical cure (eradication of liver hypnozoites) following treatment of *P. vivax* malaria (*Abstract #314*). When used in chemoprophylaxis, its long half-life is likely to allow long-interval dosing: following a loading dose there are protective levels for 10 weeks. In semi-immune Thai soldiers, a loading dose of 500 mg daily for three days followed by a monthly dose of 500 mg was highly effective in preventing both *P. vivax* and multi-drug-resistant *P. falciparum* (*Abstract #845*). The drug acts as a causal prophylactic and is schizonticidal and gametocidal. The issues of hemolysis in G-6-PD deficiency and development of methemoglobinemia also apply to tafenoquine. While more Phase III trials are needed, this agent has promise particularly for prophylaxis of malaria, and could lead to a prophylactic regimen that would only need to be administered before travel. ❖

Suggested Reading

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Plague in Madagascar—Maybe Closer, Maybe Soon?

ABSTRACT & COMMENTARY

Synopsis: *Recent reports from both the highlands and port cities of Madagascar point to an ongoing epidemic of urban and sylvatic plague in Madagascar. Bubonic plague may be difficult to recognize clinically and progression to pneumonic plague not only increases mortality but also transmission to unwary contacts. Travel medicine specialists must be aware that increasing travel to Madagascar could bring imported plague to our clinics for rapid evaluation and therapy.*

Source: Ratsitorahina M, et al. Epidemiological and diagnostic aspects of the outbreak of pneumonic plague in Madagascar. *Lancet* 2000;355:111-113.

This report describes an outbreak of pneumonic plague in Madagascar, which occurred during 1997, when an index patient with secondary pulmonary disease infected a traditional healer and his family. Upward of 2000 cases of plague had been reported annually in Madagascar recently, but only a small percentage had been pneumonic. Most had been bubonic, but in October 1997 eight patients with suspected pneumonic plague were transferred to a provincial hospital for treatment with streptomycin. Two methods were used to detect F1 antigen: an immunocapture enzyme-linked immunoassay (ELISA) and a dipstick assay from the Naval Medical Research Center in Bethesda, Maryland. The latter is a 15-minute one-step assay, which proved to be quite specific and rapid for F1 antigen detection (so-called fraction 1 glycoprotein surface antigen detection).

The index case was a woodcutter from a district 90 km north of the capital city of Antananarivo who initially presented with both fever and tender axillary adenitis. He consulted the traditional healer in his village as his course progressed over one day to clinical pneumonic plague, including chest pain, blood-stained sputum, and cough. He died the following morning but only after the healer had incised the patient's abdomen and sucked out some blood as part of the healing process. The healer became ill in three days and died within seven days; his wife and son followed soon after. Further exposures to the healer and at funeral ceremonies resulted in 18 cases, eight of whom died. The rate of infection in this remote, previously unexposed population was 8.4%, which represented a fairly good estimate of the risk of spreading pneumonic

plague in these remote villages, having not seen plague for 50 years. Not all patients with pneumonic plague are expected to be bacteremic, hence, 10 patients, both treated and untreated, were tested for *Yersinia pestis* in sputum by culture and the organisms could be isolated from only two, whereas the F1 dipstick detected antigen in nine and the F1 ELISA detected antigen in eight.

This epidemic occurred in the remote central highlands of Madagascar, where plague is endemic, transmitted by oriental fleas living upon rats and shrews, the animal reservoirs. The use of F1 antigen assays as a mainstay for the diagnosis of suspected cases of pneumonic plague and for early chemoprophylaxis of infected contacts was evident in this outbreak.

COMMENT BY FRANK J. BIA, MD, MPH

No sooner had this report appeared in the *Lancet* early this year when Madagascar appeared in the popular press in a lead article written for the Science section of the *New York Times*.[1] The wreck of the flagship, *Adventure*, which had belonged to the infamous 17th century privateer, William Kidd, had just been located in waters just off Madagascar's east coast on the shores of Isle Ste Marie. This tropical isle and its inlets of sandy beaches was a perfect place for ships to be hauled ashore and turned on their sides to have barnacles scraped from the hull, a process known as careening—essential maintenance if pirate ships were to travel as fast as possible over open waters. Kidd took advantage of this anchorage when he turned his back on a royal commission from the British crown to fight piracy, and was transformed into a pirate himself. Ultimately, William Kidd was hanged twice in London during 1701 (the rope broke on the first try).

Yet one more reason for adventure travel to Madagascar—a destination with great allure. Travel medicine consultants must become more aware of it. Forestry students, divers, archeologists, and bird watchers are among those who must be advised about the dangers posed by both urban and sylvatic plague in Madagascar. Yet, it wasn't always so.

Plague did not become established in Madagascar until the last great pandemic of 1894, which began in Hong Kong and spread rapidly over five continents. *Y. pestis* arrived in Madagascar during this third pandemic on ships from India, which appeared in November 1898. By 1921, plague had reached the high plateau regions, causing an outbreak of pneumonic plague in Antananarivo, then disappearing from seaports and becoming established at altitudes above 800 meters throughout this region.[2]

Silent until 1994, plague reappeared in epidemic form in neighboring regions such as Mozambique, Malawi, and India. Nor has this organism proven to be a particularly stable one, genetically speaking. In less than a century, the original strain that had been introduced into Madagascar has undergone chromosomal rearrangements, leading to the emergence of new ribotypes, based upon analysis of ribosomal RNA genes. It is not known what the selective advantage of such new variants may be and how they may relate to certain geographic environments, but Madagascar now has the distinction of harboring a particularly dangerous strain of *Y. pestis*.[3]

In 1995 a clinical isolate of this organism was obtained in Madagascar from a 16-year-old boy with an inguinal bubo, high fever, delirium, and prostration. The multi-drug-resistant organism, *Y. pestis* 17/95, carried a plasmid, which could be transferred by conjugation to other isolates of this organism. It carried resistance to antibiotics commonly used to treat plague such as streptomycin and the tetracyclines. In addition, the organism produced a beta-lactamase, mediating resistance to ampicillin and an acetyltransferase, causing resistance to chloramphenicol. It was not sensitive to sulfonamides, thus not allowing for synergy, but it retained sensitivity to trimethoprim, which may have accounted for this fortunate boy's recovery. This strain also retained sensitivity to the quinolones, cephalosporins, and other aminoglycosides. Madagascar's plague surveillance has been extensive, yet no such isolates had been identified between 1926 and 1995.

The appearance of multi-drug-resistant plague is an ominous event that could lead to an unpleasant emergency patient presentation in your office setting, as was recently reported by Dr. Martin Wolfe at his Travelers Medical Service in Washington, DC.[4] He treated a 47-year-old woman who had been working as a mammalogist in the La Paz District of Bolivia and had been placed on ampicillin in Bolivia for severe headache, chills, fever, myalgias, and swelling in her right axilla but without relief. Her axillary swelling increased to the point where she could no longer move her right arm effectively and Wolfe saw her on arrival in Washington at his office. He found her to be febrile with a 2.5-cm fluctuant lymph node in her right axilla. Immediate hospitalization and aspiration of the node revealed gram-negative bipolar organisms, which were evident on a Wayson stain. *Y. pestis* grew from cultures of the node aspirate and she recovered following a 10-day course of streptomycin, until now the standard drug for treatment of all isolates of this organism. The patient had been skinning rice rats as part of her work in Bolivia and then crushing their fleas with her fingers, the likely source of her infection. This case represented

the first recognized imported plague into the United States since 1926—and surely not the last, as this emerging disease continues to reappear, but now with potentially altered antibiotic sensitivity patterns, as was the case in Madagascar.

Plague had never entirely disappeared from Madagascar after its introduction by steamboats from India in 1898, but only 20-50 cases per year were reported until 1989.[5] (*See Figure.*) Since then, a steady rise in the number of suspected plague cases has been reported, now reaching 800 to 1500 per year. No longer limited to the highland regions, plague has also reappeared in the northwest coastal town of Majunga. The introduction of both F1 antibody and F1 antigen immunodiagnostic tests has increased the number of confirmed cases two- to threefold because of their greater sensitivity. Perhaps analogous to the recent West Nile virus outbreak in New York City that was preceded by increased deaths among the city's crow population, every human outbreak of plague in Madagascar has been preceded by large numbers of rat deaths. Shrews are also infected with the vector flea, *X. cheopis*, and may be the reservoir for maintenance of plague between epidemics.

Our travelers to endemic regions of Madagascar and other geographic foci of plague activity should be instructed regarding the presence of epizootic plague,[6] avoidance of sick or dead animals, and use of repellents and insecticides, gloves, and protective clothing. Prophylactic treatment with tetracycline for seven days (2 g/d) can be given to persons with close exposure to patients with pneumonic plague or with high-risk animal exposure. Doxycycline may be more efficacious than other tetracyclines, but there are no comparative evaluations among the tetracyclines. The role for the current killed whole-cell plague vaccine is limited and it does not fully protect against primary pneumonic plague. It requires three primary inoculations, and booster doses as frequently as every six months may be necessary.[6] Should a patient arrive on your doorstep with suspected plague, respiratory isolation is appropriate if pneumonic plague is suspect. The newer immunodiagnostic tests for F1 antigen detection should be considered and no assumptions regarding sensitivity of the organism to previously first-line agents such as streptomycin or chloramphenicol should be made if future reports from Madagascar or other endemic regions indicate spread of multidrug resistance. ❖

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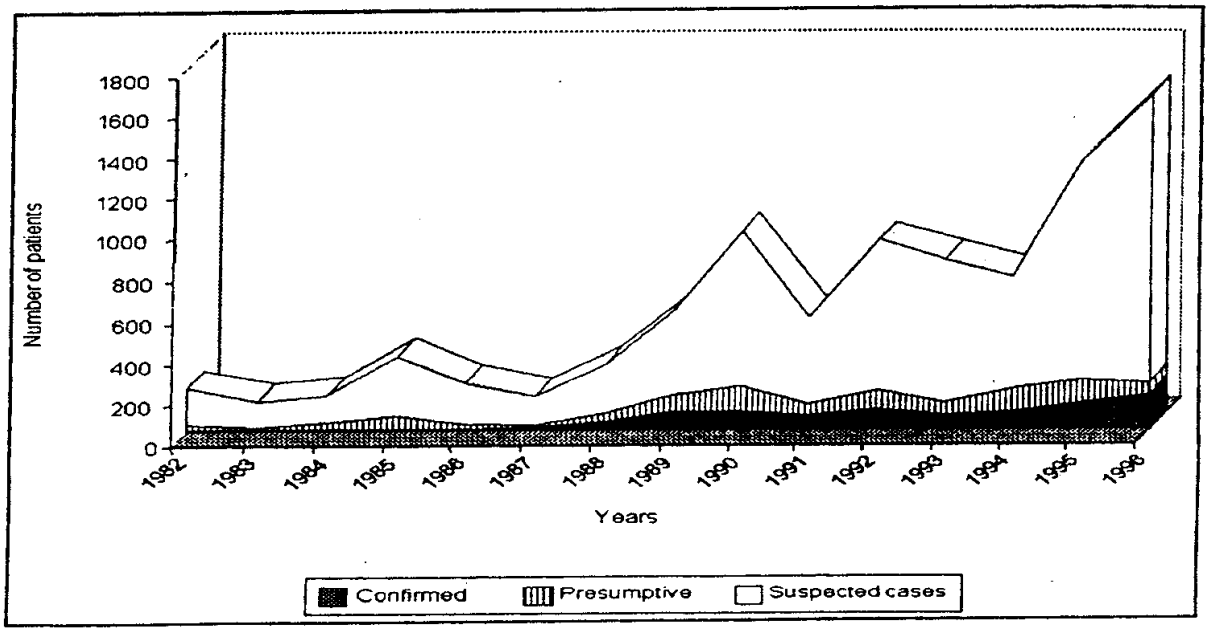
Figure

Human Plague, Madagascar, 1982-1996



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African Trypanosomiasis and Acute Pulmonary Schistosomiasis in Travelers

ABSTRACTS & COMMENTARIES

Synopsis: *Two recent articles remind us that African trypanosomiasis and acute pulmonary schistosomiasis occur in travelers from developed countries. We need to consider these diagnoses in evaluating febrile travelers returning from endemic areas.*

Sources: Sinha A, et al. African trypanosomiasis in two travelers from the United States. *Clin Infect Dis* 1999;29:840-844; Cooke GS, et al. Acute pulmonary schistosomiasis in travelers returning from Lake Malawi, sub-Saharan Africa. *Clin Infect Dis* 1999;29:836-839.

African Trypanosomiasis

Sinha and colleagues reported two travelers from the United States who contracted African trypanosomiasis during a recent safari trip in Tanzania. Both patients presented with fevers, sweats, chills, and myalgias. One patient recalled a painful fly bite six days prior to onset of her symptoms. The second patient recalled numerous tsetse fly bites and noted an expanding erythematous lesion on his right flank as well as an edematous swelling below the left lower lip. Both patients had been on malaria chemoprophylaxis. The first patient was diagnosed when the Giemsa-stained thin and thick malaria blood smears revealed trypomastigotes. The second patient was diagnosed by Wright's staining of a peripheral blood smear, which revealed trypomastigotes. The organisms were identified as *Trypanosoma brucei rhodesiense*, or the East African form of African trypanosomiasis. Cerebrospinal fluid (CSF) from both patients was examined and showed no parasites. Both patients were successfully treated with suramin.

COMMENT BY LIN H. CHEN, MD

Human African trypanosomiasis (HAT), or sleeping sickness, is endemic in sub-Saharan Africa and is caused by two subspecies of trypanosomes—*T.b. gambiense* and *T.b. rhodesiense*. Gambian HAT, also referred to as the West African form, occurs in western and central Africa, whereas Rhodesian HAT, the East African form, is endemic in eastern and southern Africa. Rhodesian HAT presents more acutely and progresses more rapidly. Sinha et al reported that since 1967, all cases of HAT occurring in U.S. travelers have been Rhodesian HAT, and most patients contracted the disease during visits to game parks.

This disease is transmitted by tsetse flies. Acute presentations may include an inoculation chancre as well as nonspecific symptoms such as fevers, headaches, myalgia, malaise, and transient edema. The patients may develop weight loss, lymphadenopathy, and splenomegaly. Late-stage manifestations include somnolence, behavior change, stupor, and coma. Convulsions are more common in children. Left untreated, the disease is fatal.

The diagnosis of Rhodesian HAT is made by demonstration of trypanosomes in blood, chancre, or CSF. Because the degree of parasitemia is higher in Rhodesian HAT than in Gambian HAT, trypanosomes are easier to detect in blood; lymph node aspirates are rarely necessary. A CSF analysis should be done whenever HAT is established or suspected, and CSF should be examined for trypanosomes with "double centrifugation." The presence of parasites, CSF pleocytosis (WBC > 5/mm^3), or Mott cells (large globular inclusion-containing plasma cells) indicates late-stage disease. Treatment of early-stage Rhodesian HAT is with suramin, and with melarsoprol when there is central nervous system (CNS) involvement.

Acute Pulmonary Schistosomiasis

Cooke and colleagues reported four patients with acute schistosomiasis presenting to John Radcliffe Hospital in Oxford, England, in 1997. All four patients swam in Lake Malawi. All four patients developed symptoms from two to eight weeks after swimming, including fevers, headaches, lethargy, cough, and urticarial rash. Laboratory evaluations were notable for eosinophilia with or without leukopenia, mild thrombocytopenia, and mild liver function abnormalities. Chest radiography and computerized tomography (CT) revealed pulmonary nodules. Only one patient was found to have *Schistosoma haematobium* in a stool sample, but all four patients had positive schistosomal serology. Although the enzyme-linked immunoassay (ELISA) did not identify the species specifically, the infections were acquired in the same area and were assumed to be *S. haematobium*. All were treated with a

single dose of praziquantel 40 mg/kg. Three of the patients experienced transient exacerbation of symptoms, but all recovered.

COMMENT BY LIN H. CHEN, MD

Schistosomiasis occurs in tropical and subtropical areas of Africa, South America, the Middle East, and East Asia. *S. haematobium* is endemic in Lake Malawi in sub-Saharan Africa, where the four travelers from the United Kingdom acquired their infection. Acute schistosomiasis is associated more frequently with *S. japonicum* and *S. mansoni* infection, and is rarely observed during *S. haematobium* infection. The article by Cooke et al indicates that acute pulmonary schistosomiasis can occur with *S. haematobium* infections, and it will be interesting to see if similar presentations continue to appear.

Schistosomiasis is acquired in fresh water, through intact skin, when the human host comes into contact with the infectious cercarial larvae. The initial contact sometimes leads to a localized dermatitis. Acute schistosomiasis (Katayama fever) may develop 4-8 weeks after exposure, with symptoms of fever, sweats, chills, cough, and headaches. The pulmonary manifestation is speculated to be an immune response to the schistosomulae. Physical signs include lymphadenopathy, hepatosplenomegaly, and rash. Eosinophilia is a significant laboratory finding.

Detection of parasite eggs in stool or urine establishes the diagnosis, but may not be present early in the course. Biopsies of the rectum, intestine, liver, prostate, or bladder can make the diagnosis if parasite ova can be demonstrated. Serologic conversion can also establish the diagnosis of acute schistosomiasis. Praziquantel is the treatment of choice for schistosomiasis, and is well tolerated.

These two articles demonstrate that travelers from developed countries can contract African trypanosomiasis and acute pulmonary schistosomiasis during travel within endemic areas. Many of the patients reported in these two articles presented with nonspecific symptoms, but the patients' history of fly bite or swimming in Lake Malawi helped a great deal in determining the diagnoses. With increased tourism to Africa, travel medicine specialists need to consider these diagnoses in febrile travelers returning from endemic areas. ❖

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CME Questions

4. Which of the following statements is *false*?

a. Infection with *Trypanosoma brucei rhodesiense* occurs in eastern Africa and causes a more acute disease than *Trypanosoma brucei gambiense*.
b. Acute schistosomiasis is usually associated with infection from *S. mansoni* and *S. japonicum* rather than *S. haematobium*.
c. When the diagnosis of African trypanosomiasis is being considered, one should perform a lumbar puncture to examine the CSF for parasites and WBCs.
d. Acute schistosomiasis should be considered in febrile patients with eosinophilia who report exposure to fresh water in Africa.
e. The history of a chancre from a tsetse fly bite should raise suspicion for possible schistosomiasis.

5. Which of the following statements regarding human plague is true?

a. Pneumonic plague is generally not transmitted from person to person, but by septicemic spread from primary bubonic plague.
b. Most isolates of *Y. pestis* from Madagascar, India, and Mozambique are now resistant to the aminoglycosides.
c. Plague in Madagascar is no longer confined to the highland plateau, but has also appeared in coastal regions.
d. Resistant plague emerging from Madagascar would best be treated with a synergistic combination of folic acid antagonists consisting of sulfonamides and trimethoprim.
e. Fluoroquinolones will have no future role in the treatment of pneumonic plague.

6. Which of the following drugs has exhibited reliable causal prophylactic activity (killing of exo-erythrocytic parasites) against *Plasmodium falciparum*?

a. Doxycycline
b. Chloroquine
c. Mefloquine
d. Azithromycin

7. Which of the following is not a precaution in the use of doxycycline in the treatment of malaria?

a. It may be taken for four weeks after leaving the malaria-endemic area.
b. It may induce photosensitivity.
c. It may induce diarrhea.
d. It may cause vaginal yeast infection.

8. Which of the following is true of acute pulmonary schistosomiasis?

a. It is acquired from freshly picked fruit.
b. Katayama fever may develop in one week.
c. A physical sign is blindness.
d. Symptoms include fever, sweats, chills, cough, and headaches.

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