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Malaria Risk in Travelers

ABSTRACT & COMMENTARY

Synopsis: *The GeoSentinel surveillance database was examined to identify patient and travel characteristics associated with the acquisition of malaria. Travel to sub-Saharan Africa and Oceania had the highest relative risk for acquisition of malaria infections. The most common reason for travel among malaria patients was to visit friends and relatives (VFR).*

Source: Leder K, et al. Malaria in Travelers: A Review of the GeoSentinel Surveillance Network. *Clin Inf Dis*. 2004;39:1104-1112.

Between November 1997 and December 2002, 1140 malaria cases were reported to and recorded within the GeoSentinel database. Sixty percent of reported malaria cases were caused by *Plasmodium falciparum,* and 24% were due to *Plasmodium vivax*. Twenty-one cases (2%) had mixed species infections. Sixty-nine percent of patients were male, and the median age was 33 years. Fever was a presenting symptom in 93% of patients with *P. falciparum* malaria, 95 % of patients with *P. vivax* malaria, 83% of those with *P. ovale* malaria, and 95% of patients with *P. malariae* malaria. Severe and/or complicated malaria occurred in 33 cases, with 3 deaths. Two of the 3 deaths were associated with malaria acquired in sub-Saharan Africa.

Most patients with malaria were travelers (39%) or immigrants/refugees (38%), followed by expatriates (12%), foreign visitors (7%), students (3%), and military personnel (0.4%). The most common reason for travel was for visiting friends and relatives (35%: VFRs), followed by tourism (26%), business (14%), immigration (10%), missionary/volunteer (9%), and research/education (5%). Only 37 % of all malaria cases had had a pretravel visit with a health care provider. Of those who were in the immigrant and VFR groups, 85% had not been seen by a health care provider prior to travel, making it unlikely that they had taken antimalarial prophylaxis.

Using a subset of patients in the GeoSentinel database who had traveled and acquired malaria during 2000-2002 and World Travel Organization data as estimates of all visitors to a region of malaria risk during the same time period, the risk per 10 million travelers of presenting to a GeoSentinel clinic with malaria was calculated. The relative risk of malaria in travelers to different regions was then calculated by comparison to the rates observed after travel to very low low-risk area such as Europe and North America. Sub-Saharan Africa (RR, 208) and Oceania (RR, 77) were associated with the greatest risk of acquiring malaria, followed by south Asia (RR, 54), Central America (RR, 38), Southeast Asia (RR, 11.5), South America (RR, 8),North Africa (RR, 7), and the Caribbean (RR, 4).

Species information was available for 1035 cases (91%). The majority (89%) of all reported *P. falciparum* cases were acquired in sub-Saharan Africa, whereas acquisition of *P. vivax* was more geographically diversified with ~30% acquired in sub-Saharan Africa, 30% from Asia, 15% from Central/South America, and 15% from Oceania.

COMMENT BY MARY-LOUISE SCULLY, MD

A potential wealth of information regarding travelers and their risk of disease acquisition is now available through the GeoSentinel database. GeoSentinel is a global sentinel surveillance network that was established in 1995 through efforts of the International Society for Travel Medicine and the Centers for Disease Control and Prevention (CDC) for collaboration in the surveillance and monitoring of travel related illnesses. At least 27 travel clinic sites on 6 continents participate in this organization. The GeoSentinel surveillance data is derived from sites and network members in both the Northern and Southern Hemispheres, and therefore, may provide new insights into global trends.

Specific information on relative risk of malaria acquisition by geographic region showed that the relative risk of malaria acquisition was greatest in the traveler to sub-Saharan Africa. Previous studies have demonstrated similar findings. In the CDC 2002 malaria surveillance data, 72.1 % of all cases were acquired in Africa, in particular, countries in West Africa.[1] Additional data from the TropNetEurop, a European surveillance network, identified similar trends with the greatest number of their infected patients acquiring their malaria in West Africa.[2] The next highest area of relative risk in the GeoSentinel data was Oceania. The CDC lists Papua New Guinea, the Solomon Islands, and Vanuatu as areas of malaria risk in Oceania.[3] The GeoSentinel data did show a greater relative risk estimate for Central America than has been previously reported. Although Leder and colleagues acknowledge that there are some limitations to the epidemiologic methods they used to calculate relative risk, the data none-the-less provide information obtained from a global surveillance network. Certainly any data on malaria risk should be interpreted with the understanding that malaria risk can often vary within designated geographic areas (ie rural vs cities, lowlands vs high altitudes, etc.), as well as with a traveler's specific itinerary (backpacking vs air-conditioned hotels), hence malaria pretravel advice should always be individualized.

Some additional insights into the types of travelers were notable. Previous studies have also shown that VFRs often return to their country of origin without seeking pretravel advice or taking chemoprophylaxis;

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the unfortunate result being the acquisition of malaria.[4,5] However, 73% of the GeoSentinel group of missionary/volunteer group did have pretravel advice, yet still acquired malaria. The need for a long duration of prophylaxis, misconceptions about risk, and development of side effects to chemoprophylaxis may have contributed to these findings in the missionary/volunteer group. Perhaps devoting extra time during pretravel consultation to reinforce the need for long term adherence to prophylaxis, and even providing alternative regimens in the event of an adverse reaction, might reduce the incidence of malaria among missionary/volunteer patients.

Lastly, we are reminded that even trips of short duration in malaria risk regions can result in disease; 37% of GeoSentinel malaria cases had travel duration of ≤ 4 weeks, and 5% had trips with durations of ≤ 1 week. In addition, 3% of patients became clinically ill while still abroad. Whereas 80% of patients with *P. falciparum* malaria presented within 4 weeks after return, only 40% of patients with *P. vivax* malaria presented within the first month. Also, patients with *P. vivax* who had seen a health care provider presented much later (median, 58 days), compared to those who did not (median, 15.5 days). Similar findings were reported using malaria surveillance data from the United States and Israel, where more than one-third of patients with *P. vivax* or *P. ovale* who had received malaria chemoprophylaxis became ill more than 2 months after their return.[6] At that point, since their return time has lengthened, patients may be less likely to attribute their symptoms of illness to their previous travel. These patients may present to local walk-in or emergency facilities where they are not known and there may be language/communication issues as well. Only a careful history by the physician to identify the possibility of previous travel to a malaria risk region can lead to the correct, potentially life saving diagnosis in these ill patients. ■

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Reducing Deaths From Malaria

ABSTRACT AND COMMENTARY

Synopsis: *Death occurred in about 1 per 100 cases of malaria diagnosed in U.S. travelers from 1963 to 2001, and many factors contribute to death from malaria. Most were preventable, and people returning home to visit friends and relatives have now become the leading risk group for malaria-related deaths.*

Source: Newman RD, et al. Malaria-Related Deaths Among U.S. Travelers, 1963-2001. *Ann Intern Med.* 2004;141: 547-555.

Newman and colleagues reviewed fatal cases of malaria that occurred from 1963 to 2001 in U.S. travelers that were reported to the National Malaria Surveillance System. Among the 185 reported cases of malaria-related deaths, 123 (66.5%) occurred in U.S. travelers, while the rest occurred in refugees, visitors, military personnel, and others. Among the U.S. travelers, there was a male predominance (60%). The majority of deaths (92.7%) were associated with 1 species, *Plasmodium falciparum*, whereas deaths due to other species occurred occasionally: *P. vivax* 3.3%, *P. malariae* 1.6%, and *P. ovale* 0.8%. The level of parasitemia with *P. falciparum* ranged from 1-60%, with a mean of level of 21.4%.

The overall case-fatality rate for U.S. travelers was 0.9%. When analyzed by species from 1985 to 2001, the case-fatality rates were: 3% for *P. falciparum*, 0.06% for *P. vivax*, 0.3% for *P. malariae*, and 0.3% for *P. ovale*. The majority of fatal cases were acquired in Africa, and were led by infections acquired in Kenya, Nigeria, and Liberia, with stays of < 1 day to 23 years; median 22 days. The main reason for travel was reported to be tourism (17.9%), followed closely by business (16.3%), missionary activities (13.8%), and visiting friends and relatives (VFR, 11.4%). However, the reasons for travel ave changed in more recent years (1989-2001), with visiting friends and relatives (VFR) as the leading reason for travel (21.3%), followed by business (19.2%), missionary work (10.6%), and tourism (8.5%).

Only 7 of 123 (5.7%) persons were found to have taken proper malaria chemoprophylaxis and

Table

Types of delays and errors

Delay or Error	Time to Action	Comment
Delay in seeking care	2-28 days, median 4.5 days	37.4% waited more than 1 day.
Delay in diagnosis	1-17 days, median 4 days	67.8% did not receive diagnosis on the day of medical visit.
Incorrect species identification		4 cases had species misidentified initially, 3 were later corrected to *P. falciparum*
Missed diagnosis		17.9% of cases were diagnosed with malaria at autopsy.
Delay in initiating antimalarial	5.5% waited 12-24 hours before	16.5% never received antimalarial.
Inappropriate antimalarial treatment		10% received inappropriate therapy for the species, region of acquisition, or treatment guidelines at the time. Chloroquine was given for falci parum malaria acquired in resistant areas; quinine and mefloquine were given in combination; sulfadoxine-pyrimethamine was given alone for severe malaria.

adhered to the regimen. Forty-six percent of the cases used no prophylaxis, 35.3% used an inappropriate drug, 4.9% were noncompliant, and data were unknown in 26%.

Clinical symptoms included fever (77.2%), chills (45.9%), mental status changes (19.7%), myalgia (18.9%), fatigue or malaise (18.0%), diarrhea, weakness, vomiting, headache, nausea, nonspecific respiratory symptoms, lethargy, cough, abdominal pain, jaundice, sweats, dizziness, anorexia, and seizures. Notably, 18.7% did not have a history of fever or chills. Onset ranged from 18 days before return to 4 years after return, with a median of 5 days following return. A case of *P. ovale* occurred 4 years after return, and a case of *P. malariae* occurred some unknown years after travel to China.

Complications included cerebral malaria (48%), renal failure (43.9%), acute respiratory distress syndrome (ARDS, 31.7%), anemia (21.1%), and disseminated intravascular coagulation (DIC, 11.4%). Splenic rupture caused deaths in 4.9% of the cases, and occurred 3-15 days after symptom onset. Newman and colleagues considered 85.4% of the malaria deaths to be preventable; 79% of cases included patient decisions that contributed to death, but 66.7% of cases involved medical errors (*see Table*).

COMMENT BY LIN H. CHEN, MD

This thorough, thoughtful analysis examined many factors that contribute to malaria-related deaths among U.S. travelers, and found the vast majority of deaths to be preventable, in spite of a decrease in the case-fatality rate of falcipaum malaria from 3.8% from a 1966-1987 study.[1] Newman et al have identified many delays and errors that contribute to the malaria deaths (*see Table*). Newman et al emphasized a number of improvements that are still necessary in order to reduce malaria-related deaths:

- Health care providers must ask about past travel history, obtain malaria smears, and establish the diagnosis of malaria in a timely fashion.
- Treatment with appropriate antimalarials must be initiated as soon as the diagnosis of malaria is made, and presumptive treatment for malaria should be started if blood smears cannot be read immediately.

•All cases of confirmed, possible, or suspected *P. falciparum* must be treated as medical emergencies.

•Hospitals must have intravenous quinidine gluconate on formulary sufficient for a 10mg/kg loading dose followed by 70 hours of continuous infusion at 0.02mg/kg/minute.

One complex issue remains. How can medical professionals influence patients to obtain pre-travel evaluation, to adhere to malaria chemoprophylaxis, and to seek medical care for illness after returning from travel? Wider publicity and education regarding malaria are needed. Travel medicine specialists possess the expertise to contribute significantly in these areas.

This study also illustrates the travel health risks for VFRs as shown previously.[2] The trend owards VFRs as the leading group of travelers to die from malaria corroborates recent studies that have found VFRs to be the leading group of travelers who acquire malaria.[3,4] In an analysis of malaria occurring in travelers in the GeoSentinel database, 85% of VFRs did not have a pre-travel encounter, and were less likely to take malaria chemoprophylaxis.[4] Similarly, VFRs are the leading group of travelers to acquire typhoid fever during their overseas visits (Reviewed in *Travel Medicine Advisor Update* 2004;14(10):53-6).[5] Education about malaria in immigrant communities may eventually lead to better acceptance of pre-travel evaluations, improved adherence to malaria chemoprophylaxis, and timely presentation for medical care of travel-related illnesses. ■

Resources

CDC 24-hour Malaria Hotline: 770-488-7788
CDC Malaria Web Site: www.cdc.gov/malaria
Eli Lilly (manufacturer of quinidine in the U.S.): 800-821-0538

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Acute Mountain Sickness Prevention: How Much Acetazolamide is Needed?

ABSTRACT AND COMMENTARY

Synopsis: *A recent study suggests that 250 mg doses of acetazolamide might be more effective than 125 mg doses in combating acute mountain sickness. Nonetheless, the applicability of these findings to travelers reaching high altitudes remains unclear.*

Source: Carlsten C, et al. A Dose-Response Study of Acetazolamide For Acute Mountain Sickness Prophylaxis in Vacationing Tourists at 12,000 Feet (3630 m). *High Altitude Medicine & Biology*. 2004;5:33-39.

Acetazolamide is commonly used as a preventive therapy in travelers going to high altitude, in an effort to decrease the risk of developing acute mountain sickness. The dosing, however, remains controversial. Carlsten and colleagues compared acetazolamide (both 125 mg and 250 mg doses) with placebo for effectiveness in altering acute mountain sickness in visitors to Bolivia.

The 33 study participants were randomized to receive placebo or either 125 mg or 250 mg of acetazolamide twice daily. Therapy was initiated *after* arrival in La Paz, Bolivia (3630 meters above sea level). Symptoms of acute mountain sickness were reported and scored using the Lake Louise questionnaire. Symptom scores were significantly lower at 24 hours than on study entry, in subjects receiving 250 mg doses than in subjects receiving 125 mg doses or placebo.

Carlsten et al conclude that "the dosing of acetazolamide for acute mountain sickness prevention in non-mountaineering tourists at altitudes below 3700 meters should not be lowered below 250 mg twice daily." They acknowledge, however, that further studies would be needed before generalizing this recommendation to other populations of travelers.

COMMENT BY PHILLIP FISCHER, MD, DTM&H

Acute mountain sickness represents a condition of uncomfortable adaptation to high altitude that is characterized by headache, along with gastrointestinal upset, fatigue, dizziness, or sleep disturbances. It is not uncommon, and occurs in about 20% of travelers to 10,000 feet elevation, and among the majority of travelers to markedly higher altitudes. The Lake Louise scoring system was developed during the early 1990s to quantitatively assess the degree of symptoms, and it is quite useful in research studies such as that conducted by Carlsten et al.

Acetazolamide is a sulfonamide carbonic anhydrase inhibitor that alters the body's acid-base, and carbon dioxide balances and stimulates some diuresis. It is widely used to prevent acute mountain sickness, and is usually given twice daily, beginning prior to ascent, and continuing for the first 3 days at altitude. Studies in travelers undergoing vigorous exercise at high altitude have documented the prophylactic value of this medication, but gastric discomfort and paresthesias have been reported. While controversial, there is some thought that lower doses (125 mg twice daily in adults) are as effective as the larger dose, and are associated with fewer side effects. Carlsten et al's study provides one attempt to determine whether or not the lower dose is as good as the more traditional 250 mg twice daily dose.

Unfortunately, Carlsten et al did not provide conclusive data to support any changes in dosing recommendations. While the subjects who received the higher dose did subsequently have a greater decrease in the Lake Louise score, several concerns make the general applicability of the finding doubtful. First, this investigation is purported to be a prophylaxis study. However, it was not initiated until the subjects were already at high altitude. In addition, the results did not show a prevention of symptoms, but rather, a decrease in symptoms.

At study entry, a significant number of subjects already qualified as having acute mountain sickness, so the design and outcome of the study seem more to have looked at therapy, rather than at prophylaxis of mildly symptomatic disease. Second, the subjects who were randomized to be in the higher dose group were more symptomatic at study entry than were the subjects in the other groups. While the paper does not indicate if there was a statistical difference between groups at baseline, it is not clear that the subsequent decrease in symptom scores was related to a differential medication effect, as opposed to the pre-treatment levels of symptoms. Finally, 1 participant was dropped from the final analysis for lack of compliance with the protocol. The published report does not state whether this non-compliance was related to side effects, and/or whether inclusion of this subject's outcome results would have altered the statistical significance of the findings.

Despite these limitations in Carlsten et al's study, the report is useful. It appropriately raises the possibility that 250 mg of acetazolamide is more effective than 125 mg, and it provides suggestive data to this end. Clearly, more study is needed. Armed with these findings, inconclusive as they are, travel medicine practitioners who currently use a 250 mg dose of acetazolamide for prophylaxis should probably avoid changing that practice until there is better support for the adequacy of the lower dose regimen. In addition, neither Ginkgo biloba, despite past optimism, nor theophylline, represents a reliably effective prophylactic agent.[1]

What else is new in the study of acute mountain sickness? The diagnosis of acute mountain sickness is based on clinically reported symptoms, and there is no accurate or objective test to predict or confirm the diagnosis. It is assumed that relative hypoxia is at the base of the pathophysiology underlying this condition, and some have used oxygen saturation as a clue to the presence of illness. O'Connor and colleagues attempted to quantify the relationship between oxygen saturation, heart rate, and acute mountain sickness in 169 hikers at 3080 meters on Mount Rainier in Washington.[2] Mean oxygen saturation was 90%, and mean heart rate was 87 per minute. At the time of evaluation, 27% of participants reported symptoms compatible with a diagnosis of acute mountain sickness. The degree of oxygen saturation, however, was not associated with symptoms of acute mountain sickness. A diagnosis of acute mountain sickness was, on the other hand, associated with a higher heart rate. The heart rate differences, while significant, were not specific enough to accurately predict a diagnosis of acute mountain sickness.

The incidence of acute mountain sickness appears to be the same in individuals across the spectrum of age. A precise determination of the degree of symptoms, however, is more difficult in pre-verbal children. Yaron and colleagues used actigraphy, a measurement of movement, and presumed sleep in 30 children aged 4-33 months.[3] Interestingly, a majority of study subjects were born prematurely, as the result of multiple gestations. Yaron et al showed that sleep disturbance was more common at high altitude (3109 meters) than at lower altitude (1601 meters), following similar travel and activity changes. The sleep pattern had returned nearly to baseline by the second night

at altitude. Clearly, altered sleep seems common in infants during the first night at high altitudes.

Thus, acute mountain sickness continues to be a problem for travelers ascending to high altitudes. Acetazolamide is the best-studied, safest, most effective medical agent for the prophylaxis of this condition, even though the optimal dose is yet to be conclusively determined. Measurements of oxygen saturation are not reliable in identifying subjects who actually have acute mountain sickness. Even young children are at risk of symptoms, and sleep disturbance is widespread in infants during the first night at altitude. ■

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A Rifaximin Review From *The Medical Letter*

ABSTRACT & COMMENTARY

Synopsis: The Medical Letter *describes rifaximin as one alternative to a quinolone antibiotic for treatment of travelers diarrhea, while noting that for severe diarrhea a fluoroquinolone is preferred.*

Source: *The Medical Letter*. Rifaximin (Xifaxan)for Travellers' Diarrhea. Vol.46 (Issue 1191) Sept 13, 2004. www.medical letter.org

By Michele Barry, MD

RIFAXIMIN (XIFAXAN®) IS A NON-SYSTEMIC RIFAMYCIN antibiotic similar to rifampin. This agent has been approved by the FDA for the oral treatment of travellers' diarrhea (TD), in patients 12 years of age or older, which is caused by enterotoxigenic *E coli*. It has been available in parts of Europe since 1987, but recently it has become more widely available in both Latin America and Asia.

Rifaximin works by binding to the beta subunit of bacterial DNA-dependent RNA polymerase, and inhibiting its action. Following oral administration, almost 97% of a dose is excreted in the feces unchanged. High concentrations are achieved within the intestinal tract that are effective against a broad range of enteropathogens, including enterotoxigenic and enteroaggregative strains of *E. coli* causing TD. It is much less active against *Campylobacter jejuni*, and there have been failures in the treatment of *Shigella flexneri* dysentery.

The agent is well-tolerated, with only a few hypersensitivity reactions that have been described, including rashes, allergic dermatitis, urticaria, and angioneurotic edema. Rifaximin is contraindicated in patients with known sensitivity to rifamycins. Although it can induce CYP3A4, there have been no significant drug interactions described, perhaps due to low systemic absorption. Rifaximin has not been studied in pregnant women, but is known to be teratogenic when injected into animals at high dose, and thus, is not recommended during pregnancy.

The dose of rifamixin suggested for TD is 200 mg TID for 3 days, and at this date, costs approximately $32.76 for 200 mg 3 times a day for the 3-day course. Only 2 relevant studies are reported in *The Medical Letter*, and one was a placebo comparison to rifaximin in 380 college students and tourists with TD in Guatemala, Mexico, and Kenya. Although microbiologic eradication rates of pathogens were similar with either rifaximin or placebo, median time to last unformed stool was statistically shorter with rifaxamin than with placebo. In a head-to-head study of rifaximin and ciprofloxacin in 187 students and tourists in Mexico and Jamaica who presented largely with enterotoxigenic *E. coli*, there was no statistical difference seen between these agents. *The Medical Letter* describes rifaximin as one alternative to a quinolone antibiotic for treatment of travelers diarrhea, while noting that for severe diarrhea a fluoroquinolone is preferred.

■ COMMENT BY MICHELE BARRY, MD

Rifaximin is a rifamycin antibacterial which has the desirable trait of not being absorbed from the gastrointestinal tract. It has been employed for prevention of surgical infection as prophylaxis during bowel surgery, for diverticular disease, and to reduce hyperammonemia in hepatic encephalopathy. The efficacy of rifaximin has been demonstrated in only a limited number of controlled clinical trials, and clearly it does not work for Campylobacter induced TD, nor is it very effective in the treatment of *Shigella flexneri* dysentery. However, when rifaximin is given for 3 days (total 1.8 grams), the fecal concentration of drug reach 8000µg/g, or more than 125 times the MIC90 for enterotoxigenic strains of *E. coli* (ETEC). Since this antibiotic will be largely excreted into the environment, *E. coli* resistance should be monitored with future use. Rifaximin is an exciting new option for the treatment of ETEC travellers' diar-

rhea, but probably should not be used for travelers with bloody diarrhea or systemic symptoms, nor should it be taken during pregnancy. ■

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CME Questions

11. Choose one false statement fromamong the following:

a. Malaria in travelers may present with vague and protean symptoms, but their disease can be complicated by cerebral malaria, acute respiratory distress syndrome, renal failure, anemia, and DIC.
b. Malaria-related deaths usually occur usually when the causative species is *P. falciparum*, but *P. vivax*, *P. ovale*, and *P. malariae* have also been associated with deaths.
c. Severe and complicated malaria should be diagnosed rapidly with a blood smear and treated with parenteral quinidine.
d. VFRs are the leading group of travelers at risk of acquiring malaria and dying from malaria in recent years.
e. Malaria is always accompanied by fever and chills as the presenting symptoms.

12. Rifaximin is superior to placebo in eradicating ETEC from the stool. True or False?

13. Rifaximin undergoes enterohepatic circulation before being excreted into feces, and thus, should not be used in pregnancy. True or False?

14. Which of the following statements regarding malaria and travelers is incorrect?

a. Travel to sub-Saharan Africa is associated with the greatest relative risk of malaria acquisition.
b. The most common reason for travel in malaria cases is traveling to visit friends and relatives.
c. Patients with *P. vivax* malaria, as opposed to *P.falciparum*,often presented later after their return, especially if they had seen a health care provider prior to their departure.
d. Missionary/volunteers were unlikely to get malaria if they had a pretravel evaluation with a health care provider.
e. Malaria risk will often vary within designated geographic areas of malaria prevalence.

15. Complete the following statement. Acute mountain sickness:

a. is more effectively prevented by 125 mg rather than by 250 mg doses of acetazolamide administered twice each day
b. is effectively prevented by Gingko biloba
c. is easily identified by pulse oximetry
d. can be observed in infants, children, and in adults.

Answers: 11. (e); 12. (false); 13. (false); 14. (d); 15. (d)