

Expert Recommendations for Antimalarial Prophylaxis

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The lack of clear guidelines for the selection and use of antimalarial chemoprophylaxis drugs has made it difficult for physicians to offer reliable protection to international travelers. Older drugs that were once the standards of treatment and prevention now face spreading drug resistance, leaving an array of antimalarials with variable safety profiles and effectiveness in different regions. Current recommendations from the Centers for Disease Control and Prevention (CDC) identify four agents (chloroquine, mefloquine, doxycycline, and atovaquone/proguanil) with broad efficacy and variable safety profiles. The World Health Organization (WHO) recommends chloroquine in combination with proguanil as an additional option. Primaquine has also been recommended by some experts as another alternative. A group of experts in travel medicine and health developed an algorithm to select an appropriate chemoprophylactic agent based on the prevalent antimalarial drug sensitivities in the travel region. The experts provided a list of key considerations—including product safety and tolerability, pre-exposure and postexposure dosing, and cost—that should be weighted before an antimalarial agent is prescribed. In conjunction with personal protective measures, the use of appropriate chemoprophylaxis offers travelers protection to counter the growing threat of malaria. Returning travelers should nonetheless be advised that despite using chemoprophylaxis, they should watch for symptoms of malaria and seek prompt medical care if febrile illness develops.

To protect against malaria, the CDC, WHO, and other authoritative bodies advise travelers to take appropriate antimalarial drug prophylaxis and to use personal protective measures against mosquito bites when traveling in endemic areas.^{1,2} However, with the continuing spread of malaria and changes in drug sensitivity, standard recommendations for antimalarial chemoprophylaxis have changed over the last decade, making it difficult

for physicians to offer a uniform approach to protection of international travelers.³⁻⁵ When chloroquine was the sole agent to prevent and treat the disease, malaria prophylaxis was straightforward. Today, the spread of drug resistance and the growing number of available antimalarial drugs make the choice of a prophylactic drug more complex. Compounding this difficulty is a lack of consensus by the various international and national health authorities regarding appropriate prophylaxis.^{1,2}

In view of the need to provide travelers with reliable advice,⁴ this article proposes a set of recommendations for antimalarial prophylaxis. In addition to emphasizing the need for personal protective measures, the recommendations identify antimalarial agents that may be used to provide prophylaxis against the various patterns of drug resistance among *Plasmodium* species. The recommendations also consider the traveler's perspective by addressing drug safety and tolerability, duration of pre-exposure and postexposure dosing, convenience of dosing, and cost in selecting agents for prophylaxis. The final component of ensuring the person's health is to maintain surveillance for emerging malaria symptoms after the traveler returns.

Personal Protective Measures for Travelers

Because no antimalarial is 100% effective, avoiding exposure to mosquitoes in endemic areas is an essential adjunct to any prophylactic regimen (Table 1). Physicians should review these specific measures with travelers during pretravel consultations and emphasize the importance of personal protection in preventing malaria.

Since the malaria vector, the female of *Anopheles* spp mosquitoes, feeds primarily from dusk until dawn,⁶ travelers can reduce their risk of infection by limiting evening activities, particularly outdoor activities. Travelers who take day trips from malaria-free cities or resorts to the countryside are at minimal risk provided they return to the city before dusk.⁷

If they are outdoors after sunset, travelers should try to wear long-sleeved shirts and long pants to limit the amount of exposed skin.⁶ Because insects prefer landing on dark surfaces, light-colored clothing is recommended.⁸ Applying an insecticide such as permethrin to clothing provides further protection.⁹ Sprayed on clothing, permethrin remains effective for several weeks, even after laundering.¹⁰

It is also strongly encouraged that topical insect repellent be applied to exposed skin, especially between

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Table 1 Personal Protective Measures Against Malaria*

1. Wear long-sleeved shirts and long pants (weather permitting).
2. Apply insect repellent containing DEET to exposed skin.
3. Spray “knock-down” insecticides containing pyrethrins onto clothing.
4. At dusk, spray living and sleeping areas with “knock-down” insecticides (e.g., those containing pyrethrins).
5. Sleep in well-screened or airconditioned rooms.
6. Use bed netting of small mesh and good quality impregnated with permethrin.
7. Use mosquito coils or vaporizing mats containing pyrethroids.

*Used in conjunction with chemoprophylaxis.

DEET = diethyltoluamide.

Adapted from Wyler DJ.⁴

dusk and dawn.^{1,2,8} Products containing diethyltoluamide (DEET) are considered to be most effective.^{1,6} Depending on the formulation, insect repellent must be reapplied every 4 to 8 hours.^{6,11}

In one large survey of European tourists visiting East Africa, sleeping in airconditioned rooms was found to significantly reduce the incidence of malaria ($p = .04$).⁸ Use of electric fans may also reduce risk, although this has not been proven definitively.⁸

Those travelers who are not staying in well-screened or airconditioned rooms should spray living and sleeping areas with a pyrethroid-containing insecticide for flying insects (e.g., ordinary flying insect sprays like Raid) during the evening and nighttime hours to kill any insects that may have entered the room during the day.^{1,6} Burning mosquito coils or candles formulated with mosquito repellents or using electric mats that vaporize pyrethroid insecticides also may help avoid overnight exposure to insects.^{1,2,6} Insect “zappers” or electrocuters are not effective.⁸

Travelers who are not staying in airconditioned or well-screened rooms should take the additional precaution of sleeping under bed nets (mosquito netting). Insecticide-treated (with permethrin or deltamethrin) bed nets are significantly more effective than untreated nets and are safe for children and pregnant women.⁶ In a meta-analysis of multiple randomized controlled trials, nets sprayed with permethrin proved to reduce the number of episodes of malaria by 39% and child mortality by 83% among residents of endemic areas compared with those who used no nets or untreated nets.^{8,12} Nets should extend to the floor or be tucked under the mattress to prevent access by mosquitoes.

Antimalarial Drug Prophylaxis for Travelers

The growing list of antimalarials has made the choice of a prophylactic drug more complex in recent years. Without standard recommendations for selecting an antimalarial agent, numerous factors about individual drugs must be considered in addition to efficacy,

including safety, dosing, cost, and patient preference. Indeed, these latter considerations ultimately will determine any given patient’s compliance with the regimen and hence the effectiveness of these drugs.¹⁰

The spread of *Plasmodium falciparum* resistant to chloroquine and other antimalarials has significantly affected antimalarial chemoprophylaxis decisions over the past decade. Chloroquine resistance is now widespread in most malaria-endemic regions of the world, and *P. falciparum* resistance to other antimalarials, including multidrug resistance, has been reported.⁶ In addition to the threat of drug resistance, the potential for adverse effects must be considered. Whereas chloroquine, the former standard, is generally well tolerated, some antimalarials have the potential to cause severe adverse reactions.⁴ Moreover, even minor side effects may cause some patients to discontinue or interrupt their chemoprophylaxis, leaving them unprotected against infection.^{4,7} Poor compliance with chemoprophylaxis has been identified as a significant risk factor for malaria among travelers.¹⁰ Other factors that influence compliance with prophylaxis and therefore the risk for malaria include the convenience of the prophylaxis regimen (daily versus weekly administration), the duration of pre-exposure and postexposure dosing, and cost.

These issues were addressed by travel medicine experts in formulating a set of recommendations for antimalarial prophylaxis for travelers. The goal is to simplify the decision-making process for practitioners. From the range of available antimalarials, the choice of drugs was narrowed to those showing the broadest efficacy, a low potential for side effects, and availability in the United States. Four drugs were selected for use: chloroquine, mefloquine, doxycycline, and atovaquone/proguanil.¹ Primaquine, used as a chemoprophylactic agent, will not be discussed in this review because it is not approved for this use in most countries. It is, however, felt by many to be a second line drug to be used in chloroquine resistant areas when other drugs cannot be used. The combination of chloroquine and proguanil has not been considered because it has been shown to

be considerably less effective than the above agents (except for chloroquine alone) and has not been studied widely outside of Africa. The algorithm, shown in the Figure, represents a consensus among these travel medicine experts concerning the prophylaxis of malaria. As outlined in the algorithm, the first consideration when choosing an agent for any traveler at substantial malaria risk involves the drug sensitivity of parasites in the travel destination.

Travel to Chloroquine-Sensitive Areas

For sensitive *P. falciparum*, chloroquine remains the drug of choice to prevent malaria. Chloroquine is inexpensive, fast-acting, and widely available. The usual doses are generally well tolerated and are safe for pregnant women and children.^{1,7}

Because of widespread resistance, however, the use of chloroquine against *P. falciparum* malaria is limited to

persons traveling in Central America, the Caribbean, and parts of the Middle East. Current information on drug sensitivity in a particular country or region can be found on the CDC Web site listing of regional malaria information, <<http://www.cdc.gov/travel/regionalmalaria/index.htm>>, or can be obtained by fax request at 1-800-232-3299, document no. 000005.^{1,6} Although chloroquine remains effective against most strains of *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae* as well,¹³ resistance of *P. vivax* is increasing, particularly in the South Pacific, Southeast Asia, and parts of South America (Guyana).⁶

For prophylaxis, the adult dosage is 500 mg of chloroquine phosphate (300 mg base) given orally once weekly (Table 2). For children, dosing is based on body weight, with 5 mg base given per kilogram of body weight up to the adult dose.^{1,14} The drug is taken once weekly and should be taken with food if nausea occurs.

**PROPHYLAXIS OPTIONS*†
BY AREA OF ANTIMALARIAL SENSITIVITY**

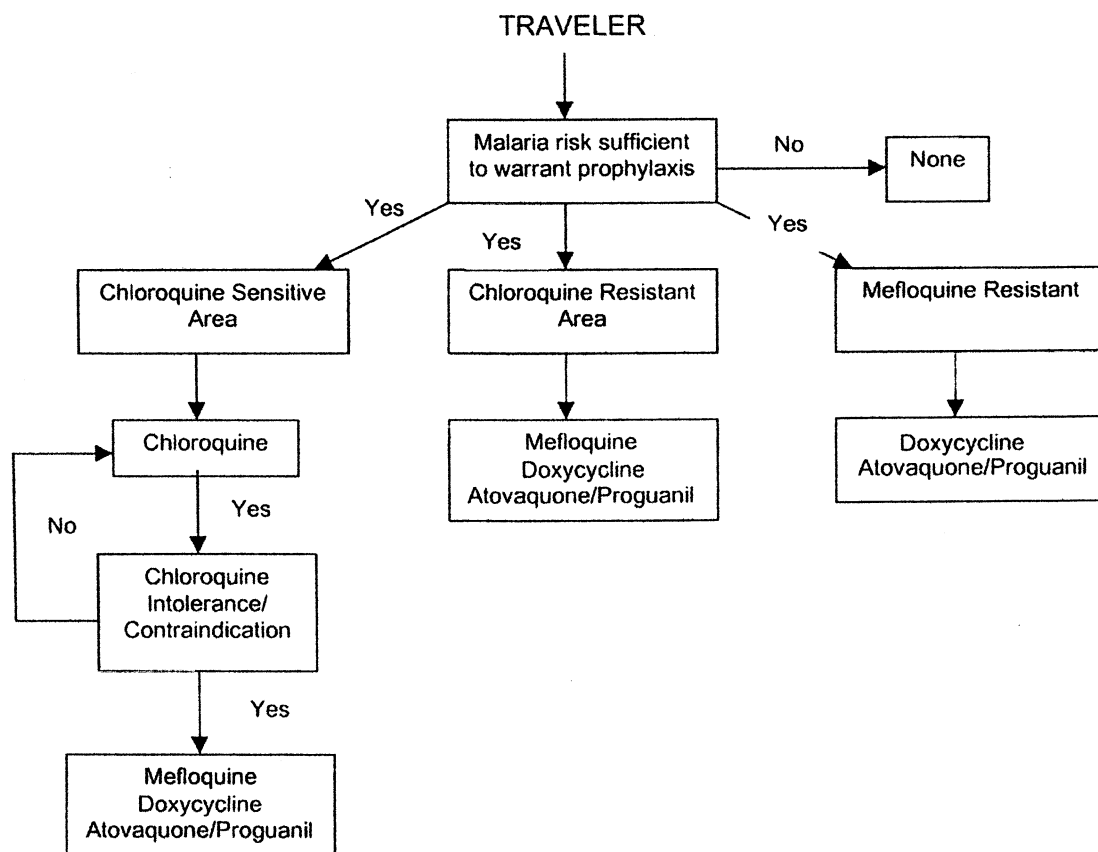


Figure Antimalarial prophylaxis options based on drug sensitivity within travel destination.

*Drugs are not listed in order of preference. They are listed in temporal order of clinical experience for malaria prophylaxis. Current CDC recommendations state that mefloquine, doxycycline, and atovaquone/proguanil are all options for malaria prophylaxis (unless otherwise contraindicated).

†Clinicians also should refer to Table 4 to review contradictions for each drug.

Table 2 Recommended Dosages for Antimalarial Prophylaxis^{1,13}

Drug	Adult Dosage	Child Dosage	Pre-exposure and Postexposure Dosing
Chloroquine	500 mg salt (300 mg base), orally once weekly	5 mg base/kg body weight, orally once weekly, up to the adult dose	Start 1–2 weeks before travel to malarious region; continue for 4 weeks after departure
Mefloquine	250 mg salt (228 mg base), orally once weekly* Take with food.	Adjusted to body weight, all given orally once weekly: <15 kg: 5 mg/kg salt (4.6 mg/kg base) 15–19 kg: ¼ tablet 20–30 kg: ½ tablet 31–45 kg: ¾ tablet >45 kg: 1 tablet	Start 1–2 weeks before travel to malarious region; continue for 4 weeks after departure
Doxycycline†	100 mg orally once daily Take with food	>8 yrs: 2 mg/kg orally once daily, up to adult dose	Start 1–2 days before travel to malarious region; continue for 4 weeks after departure
Atovaquone/ proguanil‡	250 mg atovaquone/ 100 mg proguanil (1 tablet) orally once daily Take with food or milk	Adjusted to body weight, all given orally once daily: 11–20 kg: 62.5/25 mg (1 pediatric tablet) [§] 21–30 kg: 125/50 mg (2 pediatric tablets) 31–40 kg: 187.5/75 mg (3 pediatric tablets) >40 kg: 250/100 mg (1 adult tablet)	Start 1–2 days before travel to malarious region; continue for 1 week after departure

*In countries other than the United States, mefloquine tablets contain 250 mg mefloquine base.

†Doxycycline is not recommended for use in pregnant or lactating women or in children under the age of 8 years because of toxicity to bone and tooth development.

‡Atovaquone/proguanil is not recommended for use in pregnant women, in women breast-feeding infants <11 kg, or in infants <11 kg.

§Pediatric tablets of atovaquone/proguanil contain 62.5 mg atovaquone/25 mg proguanil.

Prophylaxis should be started 1–2 weeks before travel to a malarious area and continue for 4 weeks after departure from the area.¹

Although chloroquine is usually well tolerated with only minor side effects, some persons may not tolerate it or may have specific contraindications to its use. For these persons, any of the three other recommended drugs (mefloquine, doxycycline, or atovaquone/proguanil) may be prescribed. The choice among these options is discussed below.

Travel to Chloroquine-Resistant Areas

For travel to areas where chloroquine-resistant *P. falciparum* is prevalent, three drugs are recommended as effective alternatives to chloroquine: mefloquine, doxycycline and atovaquone/proguanil. These three drugs are also currently considered the primary options for antimalarial chemoprophylaxis in the CDC recommendations.¹ The choice of an agent for a particular region or patient depends on several factors, including regional drug sensitivity, drug tolerability, and convenience of dosing. Table 3 compares the recommended antimalarials on the

basis of their dosing, discontinuation rate due to adverse events, and cost.

Mefloquine. Available in Europe since 1985 and in the United States since 1990,¹⁵ mefloquine has been commonly prescribed for travelers to most chloroquine-resistant areas.^{1,6} However, resistance to mefloquine has emerged in Southeast Asia along Thailand's borders with Cambodia and Myanmar (Burma), and rare cases have appeared in Africa and South America.^{6,15}

In prophylactic doses, mefloquine is generally well tolerated, with adverse effects that are similar in frequency and severity to those seen with chloroquine. Approximately 25–40% of users experience side effects with mefloquine, most of them mild and self-limited (e.g., nausea, dizziness, headaches).^{6,15} A recent meta-analysis of controlled clinical trials has shown that, except for a higher incidence of insomnia and fatigue, overall rates of adverse effects and withdrawals from mefloquine therapy are not significantly higher than those for chloroquine or doxycycline.¹⁶ Reports about potentially serious adverse events that have appeared in the lay press have been exaggerated and are not consistent with the results of numerous randomized placebo controlled trials; how-

Table 3 Factors that Influence Antimalarial Prophylactic Drug Choice*

Factors	Chloroquine	Mefloquine	Doxycycline	Atovaquone/proguanil
Dosing/administration	Once weekly	Once weekly	Once daily	Once daily
Pre-exposure dosing	7–14 days	7–14 days	1–2 days	1–2 days
Postexposure dosing	4 weeks	4 weeks	4 weeks	1 week
Drug discontinuation due to adverse events	NA	2–5%	NA	<1%
Cost for 2 weeks of travel*	\$40.32	\$65.76	\$4.40 [†]	\$86.24

*Cost based on average **wholesale** price as of August 2001, USD.

[†]Cost of generic doxycycline.

NA = not available.

ever fear of these side effects has caused some travelers to refuse the drug or to discontinue treatment.⁶ The risk of serious neuropsychiatric adverse events (severe anxiety, depression, psychosis, convulsions) is very low with prophylactic doses.⁶

The drug is contraindicated for patients with a history of epilepsy or seizures, serious psychiatric illness, or cardiac conduction disturbances associated with arrhythmia (Table 4).^{1,6} Mefloquine is safe for children and pregnant women in their second or third trimester, but the manufacturer indicates that it should be used cautiously in the first trimester.^{6,13}

For prophylaxis, the adult dosage of mefloquine is 250 mg salt (one tablet) taken orally once weekly. The dosage for children should be adjusted by body weight (see Table 2). Prophylaxis should start 1–2 weeks before travel and continue for 4 weeks after departure from the malarious area.¹

Doxycycline. Doxycycline is a second option for antimalarial prophylaxis in chloroquine-resistant areas. The drug is dosed daily and offers excellent protection against infection by *P. falciparum*, even in areas with multidrug-resistant strains.⁶ It is an effective alternative for travelers who are unable to tolerate mefloquine or atovaquone/proguanil in chloroquine-resistant areas. As with many medications, strict compliance with the dosing regimen is needed to obtain maximum efficacy.¹⁷

Doxycycline can be associated with side effects that include phototoxicity, nausea, esophagitis, and vaginal candidiasis. Because of the potential phototoxicity reaction, sunscreen containing ultraviolet A (UVA) protection should be recommended.^{1,7} Doxycycline is contraindicated in pregnant and lactating women and in children younger than 8 years of age because of toxicity to bone and tooth development.⁸ Women susceptible to vaginal candidiasis should carry an over-the-counter antifungal drug.^{1,7} For prophylaxis, adults should receive 100 mg orally once daily. Children older than 8 years are dosed according to body weight (see Table 2). Prophylaxis should begin 1–2 days before a person enters the malarious area, and continue for 4 weeks after leaving the area.^{1,14}

Atovaquone/proguanil. Atovaquone/proguanil, the most recently approved antimalarial, is considered the drug of choice for travelers taking relatively brief trips to chloroquine-resistant areas because of its favorable safety profile, its short period of pre-exposure and postexposure dosing, and its cost/benefit ratio. Its favorable safety profile needs to be considered in the context of its recent availability; atovaquone/proguanil has only been commercially available for less than 2 years. In multiple trials, atovaquone/proguanil has been shown to be effective against both chloroquine-resistant *P. falciparum* and multidrug-resistant strains in semi-immune residents of malaria-

Table 4 Major Contraindications for Antimalarial Prophylactic Drugs

	Chloroquine	Mefloquine	Doxycycline	Atovaquone/proguanil
Seizure disorder	No	Yes	No	No
Cardiac conduction disturbance	No	Yes	No	No
History of depression, mental illness	No	Yes	No	No
Drug phototoxicity potential	No	No	Yes	No
Yeast infections	No	No	+/-*	No
Pregnancy	No	No	Yes	Unknown
Pediatrics	No	No	Yes	No
Hepatic insufficiency	Yes	No	Yes	No
Renal insufficiency	No	No	Yes	Yes

*Relative precaution.

hyperendemic areas. In these studies, protective efficacy rates ranged between 95–100%.^{18–22} However, data are not yet available on the protective efficacy of this drug combination in nonimmune travelers from industrialized countries. Because of its effectiveness against multidrug-resistant strains, atovaquone/proguanil may offer improved protection in areas where *Plasmodium* spp demonstrate changing patterns of reduced drug sensitivity, for example, along the borders of Thailand where multidrug resistance occurs.^{10,23}

Side effects with atovaquone/proguanil tend to be uncommon and include abdominal pain, nausea, vomiting, and headache.¹ Atovaquone has been used since 1992 to treat *Pneumocystis carinii* pneumonia; at the higher daily doses required for pneumocystic pneumonia, the drug has a history of good tolerability with very low rates of serious adverse events.²⁴ Proguanil, which has been widely used since the 1940s to prevent and treat malaria, is considered one of the safest antimalarials,²³ with few, mild side effects, and no serious toxicity even in cases of overdosage.^{13,24} There are relatively few contraindications to the use of atovaquone/proguanil (see Table 4) (although, due to lack of data, the drug is not currently recommended for use in pregnant women, in women breast-feeding infants who weigh less than 11 kg, or to treat infants less than 11 kg).¹

Since atovaquone/proguanil is active against liver-stage parasites (i.e., causal prophylaxis), it requires only a short period of pre-exposure and postexposure dosing.²³ Atovaquone/proguanil requires only 1 week of dosing after leaving endemic areas.²³ Other antimalarials (except for primaquine) require 4 weeks of postexposure dosing, which may lead to compliance problems.¹⁰ The short period of postexposure dosing with atovaquone/proguanil is ideal for frequent travelers and those who live in the tropics and have repeated short exposures outside of urban areas. For adults, the prophylactic dosage of atovaquone/proguanil is one tablet (250 mg atovaquone/100 mg proguanil) orally, once daily. For children who weigh more than 11 kg, doses vary by body weight (see Table 2). To enhance drug absorption, atovaquone/proguanil should be taken with food or milk.¹

Prophylaxis in Pregnancy and in Children

Because of their restricted chemoprophylactic options, malaria poses special risks for pregnant women. Falciparum malaria is particularly dangerous and carries an even higher risk of morbidity and mortality in pregnant women than it does in the general population. Severe and complicated malaria may occur, as may fetal loss and maternal death.^{6,10}

Both the CDC and WHO advise against travel to endemic areas during pregnancy.^{1,2} If travel cannot be postponed, great care should be taken to avoid mosquito bites (see Table 1). In addition, pregnant women should employ antimalarial chemoprophylaxis, using one of the antimalarials that have demonstrated safety in pregnancy.^{1,2,10}

For travel to chloroquine-sensitive areas, the CDC recommends that prophylaxis for pregnant women be given with chloroquine or hydroxychloroquine sulfate, using the typical adult doses (see Table 2).¹ In chloroquine-resistant areas, mefloquine may be given during the second or third trimesters, but limited data exist regarding its safety during the first trimester.² A large post-marketing study of women exposed to mefloquine before or during pregnancy showed the rate of congenital malformations was no different than that of the general population.²⁵

The use of doxycycline is contraindicated during pregnancy because of the risk of toxicity to developing bones and teeth in the fetus. Atovaquone/proguanil has not been tested adequately in pregnant women and, therefore, its use has not been recommended.¹ However, neither component drug has shown teratogenic effects in animal models, and the manufacturer suggests that the drug may be used cautiously if the potential benefit outweighs the potential risk to the fetus.¹⁹

Although both chloroquine and mefloquine are found in breast milk, they are considered safe for infants.

Malaria is also of special concern for infants because of its high mortality rate. Although direct data are lacking, drugs that are safe for pregnant women are generally considered safe for infants, albeit in reduced dosages.¹⁰ Again, chloroquine or hydroxychloroquine may be used in chloroquine-sensitive areas, with atovaquone/proguanil (for infants who weigh more than 11 kg) or mefloquine used in chloroquine-resistant areas (see Table 2). Doxycycline should not be used in children younger than 8 years.¹ Because of the bitter taste of these drugs, parents may need to mix the drug with something like applesauce, chocolate syrup, or jelly.¹

Special Considerations in Clinical Practice

Concurrent medical conditions and patient specific factors, including patient preference, need to be considered when choosing an antimalarial agent. A complete medical evaluation is essential to ensure appropriate chemoprophylaxis is prescribed. With all antimalarials, prior patient experience is a key consideration. To help ensure compliance, patients who admit to a negative experience with an agent should be switched to an appropriate alternative. The following recommenda-

tions are intended to simplify clinical decision-making for practitioners.

Travel Destination

In travelers to Central America, the Caribbean, and parts of the Middle East where *P. falciparum* is sensitive to chloroquine, this agent should be prescribed except for patients with hepatic insufficiency (see Major Contraindications section to follow). For travel to Southeast Asia, particularly Thailand's borders with Cambodia and Myanmar (Burma), doxycycline or atovaquone/proguanil is recommended due to emerging resistance to mefloquine.

Pre-exposure/Postexposure Dosing

In clinical practice, mefloquine, doxycycline, and atovaquone/proguanil, are recommended for travel to chloroquine-resistant malarious areas. Only doxycycline and atovaquone/proguanil are recommended for 1–2 days pre-exposure dosing. However, with almost 20 years of experience with mefloquine use by last minute travelers, the drug has been shown to be very effective even when taken just prior to exposure. For repeat business or personal travelers who prefer not to take prolonged courses of antimalarials after departure from malarious areas, atovaquone/proguanil or primaquine should be considered because of their 1-week postexposure dosing regimen.

Major Contraindications

Patient medical history and comorbid conditions should be evaluated prior to prescribing an antimalarial agent. In patients with hepatic insufficiency, mefloquine or atovaquone/proguanil can be prescribed. In renal insufficiency, for travelers to chloroquine-sensitive regions, chloroquine can be used, and for travel to chloroquine-resistant areas, mefloquine should be prescribed. If patients with renal impairment cannot tolerate or choose not to take mefloquine, doxycycline or atovaquone/proguanil can be used with caution.

In patients with a history of photosensitivity, consideration should be given to mefloquine or atovaquone/proguanil over doxycycline. Mefloquine is contraindicated in patients with history of cardiac conduction abnormalities, depression or mental illness, or seizure disorder. In the presence of these conditions and depending on travel destination, chloroquine, doxycycline or atovaquone/proguanil may be prescribed.

Cost of Therapy

When assessing antimalarial therapy, cost and compliance are two issues to discuss with patients. Several factors, including tolerance of side effects, patient dosing preference, and cost combine to determine the relative

value of a medication. Cost is a significant factor in the choice of antimalarials for the majority of those who travel for more than 2 weeks, especially for budget travelers and immigrants returning to their homelands to visit family and friends. The problem is multiplied for families that include one or more children or grandparents. If overall cost is a concern, doxycycline may be the best option, followed in order of cost by primaquine, mefloquine, and atovaquone/proguanil.

For short duration travel (≤ 2 to 3 weeks) or if cost is less of a concern (e.g., business travelers or those with a drug plan), mefloquine and atovaquone/proguanil are appropriate recommendations. Since the cost of antimalarials may vary considerably from country to country or from continent to continent, discussions on the subject of cost must take into consideration local circumstances.

Surveillance for Emerging Illness After Travel

No antimalarial chemoprophylaxis regimen is 100% effective, and travelers may develop malaria despite perfect compliance.¹⁰ In practice, however, many patients may discontinue their antimalarial drug because of side effects without discussing it with their physician and thus place themselves at risk for infection.¹⁰

Symptoms of malaria, which include fever, shaking chills, headache, muscle aches, and fatigue, may occur as early as 1 week after infection. Most travelers who acquire *P. falciparum* infection develop symptoms within 2 months of exposure, but other types of malaria, especially that caused by *P. vivax*, may occur months to 1–2 years after travel.^{1,6}

Delays in the treatment of *P. falciparum* malaria, which can be rapidly fatal, are associated with increases in serious disease-related morbidity and mortality.^{5,26} The most important factors that determine patient survival are early diagnosis and prompt therapy.⁶ Travelers should be made aware of the symptoms of malaria and strongly encouraged to seek prompt medical care if febrile illness develops after they return from an endemic area. They should also be told to have three thick and thin blood films done before the diagnosis of malaria is ruled out. Health care providers should be cognizant of the risk of malaria in the differential diagnosis of illness in returned travelers.⁵

Conclusions

The continuing spread of malaria beyond endemic areas and the emergence of drug-resistant strains have complicated decision making regarding antimalarial prophylaxis for travelers. Older drugs that were once the standards of treatment and prevention now face reduced

effectiveness, leaving physicians to choose among an array of other drugs, some with less favorable safety profiles or unclear patterns of resistance. In addition, in the absence of uniform guidelines, the place of newer anti-malarial drugs in the overall strategy of antimalarial prophylaxis has been unclear.

These new recommendations attempt to simplify the decision-making process for practitioners. They provide a selected list of agents with broad efficacy and limited safety concerns and present a clear algorithm for selecting the appropriate agent based on the prevalent drug sensitivity in the travel region. In conjunction with proper personal protection measures, appropriate chemoprophylaxis offers travelers reliable protection against infection by *Plasmodium* spp. The current recommendations offer physicians an important starting point for identifying the appropriate agent to assure the safety of travelers.

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