CHAPTER 6

Malaria Prevention

Hans D. Nothdurft and Kevin C. Kain

Access evidence synopsis online at ExpertConsult.com.

Malaria is the most important parasitic disease in the world. Human malaria is a blood-borne protozoal infection caused by five species of the genus *Plasmodium*: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*. The infection is transmitted through the bite of infected female *Anopheles* mosquitoes. Less commonly, malaria may be transmitted by blood transfusion, with shared needle use, or congenitally, from mother to fetus. Ecologic change and economic and political instability, combined with escalating malaria drug resistance, have led to a worldwide resurgence of this parasitic disease. The 2014 World Malaria Report (World Health Organization [WHO] and United Nations Children's Fund [UNICEF]) estimated there were more than 220 million cases and more than 600,000 deaths annually resulting from malaria.

Malaria is not just a problem in the developing world, however. The combination of increases in international travel and increasing drug resistance has resulted in a growing number of travelers at risk of contracting malaria. It is estimated that as many as 30,000 travelers from industrialized countries contract malaria each year. However, this incidence is likely to be an underestimate because of the failure to take into account those who are diagnosed and treated abroad and the prevalence of underreporting. The majority of *P. falciparum* cases imported into North America and Europe are acquired in Africa (85%), and travel to the African continent is still on the rise.

The overall case fatality rate of imported *P. falciparum* malaria varies from 0.6 to 3.8% but may be much higher in the elderly. The fatality rate of severe malaria may be ≥20% even when managed in modern intensive care units; however, cases of imported malaria and associated fatalities remain largely preventable, provided high-risk travelers use appropriate chemoprophylaxis and measures to reduce insect bites, and physicians promptly recognize infections and initiate appropriate treatment.

APPROACH TO MALARIA PREVENTION

This chapter highlights the important principles of malaria prevention. The interested reader is referred to **Table 6.1** and the references for additional sources of information and country-specific malaria risk. There are four principles—adapted from the WHO's ABCD of malaria protection—of which all travelers to malarious areas should be informed:

A Be **A**ware of the risk and the symptoms and understand that malaria is a serious infection.
B Avoid mosquito **B**ites.
C Take **C**hemoprophylaxis when appropriate.
D Seek immediate **D**iagnosis and treatment if fever develops during or after travel.

These principles, which are key issues to be considered when advising travelers on protection against malaria, are discussed in further detail below and summarized as a checklist in **Table 6.2**.

Protection against malaria can be summarized into the following four principles.

TABLE 6.1 Internet Resources for Travel Health Information and Country-Specific Malaria Risk

http://www.cdc.gov/travel/ US Centers for Disease Control and Prevention (Travelers' Health Section)	On-line references include full text of Health Information for International Travel 2016, with full adult and pediatric recommendations, including malaria risks and recommendations.
http://www.who.int/ith/en WHO (International Travel and Health Information Resource Page)	Includes updates on country-specific malaria risk.
www.TravelHealth.gc.ca Health Canada (Travel Medicine Resource Page)	See Information for Travel Medicine Professionals. Contains CATMAT guidelines, travel bulletins, and updates for preventing and treating malaria in travelers.

CATMAT, Committee to Advise on Tropical Medicine and Travel.

1. Assessing Individual Risk

Estimating a traveler's risk is based on a detailed travel itinerary and specific risk behaviors of the traveler (examples in parentheses represent increasing risk). The risk of acquiring malaria varies according to the geographic area visited (e.g., Southeast Asia vs. Africa), the travel destination within different geographic areas (urban vs. rural travel), type of accommodations (well screened or air conditioned vs. camping), duration of stay (1-week business travel vs. 3-month overland trek), season of travel (low vs. high malaria transmission season), and elevation of destination (malaria transmission is rare above 2000 m). In addition to the location, travelers can influence their own risk by how well they comply with preventive measures, such as treated bed nets and chemoprophylactic drugs, and the efficacy of these measures.

Additional information can be obtained from studies using malaria surveillance data that estimate risk of malaria in travelers. For example, relative risk assessments show that travelers are 207 times more likely to acquire malaria in sub-Saharan Africa compared with low-risk areas, and the relative risk decreases with other destinations studied such as South Asia (53.8), Central America (37.8), Southeast Asia (11.5), and South America (8.3). Risk of infection if no chemoprophylaxis is used varies from >20% per month in regions of Papua (formerly Irian Jaya) to 1.7-2.4% per month in West Africa to 0.01% per month in Central America. Of note, the estimated risk of malaria for travelers to Thailand in one study was 1:12,254, which may be less than the risk of a serious adverse event secondary to malaria chemoprophylaxis. Such data can also help provide an estimate of the cost/benefit ratio for the use of various chemoprophylactic drugs in different geographic areas. Good sources of updated malaria information and country-specific risk are available online from the WHO, Centers for Disease Control and Prevention (CDC), and Health Canada (Table 6.1).

2. Preventing Mosquito Bites (Personal Protection Measures)

All travelers to malaria-endemic areas need to be instructed in how best to avoid bites from *Anopheles* mosquitoes that transmit malaria. Any measure that reduces exposure to the evening and nighttime feeding female *Anopheles* mosquito will reduce the risk of acquiring malaria. Different brands of effective insect repellents are available, but some should not be used on babies and small children. Insecticide-impregnated bed nets (with permethrin or other chemicals) are safe for children and pregnant women and are—together with use of repellents—an effective prevention strategy that is underused by travelers. Additional details are provided in Chapter 1.

TABLE 6.2 Checklist for Travelers to Malarious Areas

The following is a checklist of key issues to be considered in advising travelers.

1. Risk of malaria

   Travelers should be informed about their individual risk of malaria infection and the presence of drug-resistant *P. falciparum* malaria in their areas of destination. Pregnant women and adults taking young children should question the necessity of the trip.

2. Anti-mosquito measures

   Travelers should be instructed how to protect themselves against mosquito bites.

3. Chemoprophylaxis (when appropriate)

   Travelers should be:

   a. Advised to start chemoprophylaxis before travel and to use prophylaxis continuously while in malaria-endemic areas and for 1 or 4 weeks after leaving such areas (depending on the drug used).
   b. Questioned about drug allergies and other contraindications for drug use.
   c. Informed that antimalarial drugs can cause side effects; if these side effects are serious, medical help should be sought promptly and use of the drug discontinued. Mild nausea, occasional vomiting, or loose stools should not prompt discontinuation of chemoprophylaxis, but medical advice should be sought if symptoms persist.
   d. Warned that they may acquire malaria even if they use malaria chemoprophylaxis.
   e. Warned that they may receive conflicting information regarding antimalarial drugs overseas but that they should continue their prescribed medication unless they are experiencing moderate to severe adverse effects.

4. In case of illness, travelers should be:

   a. Informed that symptoms of malaria may be mild and that they should suspect malaria if they experience a fever or flu-like illness (unexplained fever).
   b. Informed that malaria may be fatal if treatment is delayed. Medical help should be sought promptly if malaria is suspected, and a blood sample should be taken and examined for malaria parasites on one or more occasions (if possible, blood smears should be brought home for review).
   c. Reminded that self-treatment (if prescribed) should be taken only if prompt medical care is not available within 24 hours and that medical advice should still be sought as soon as possible after self-treatment.
   d. Reminded to continue to take chemoprophylaxis in cases of suspect or proven malaria.

5. Special categories:

   Pregnant women and young children require special attention because of the potential effects of malaria illness and inability to use some drugs (e.g., doxycycline).

Adapted from World Health Organization, 2012, International Travel and Health.

3. Use of Chemoprophylactic Drugs Where Appropriate

The use of antimalarial drugs and their potential adverse effects must be weighed against the risk of acquiring malaria (as described previously). The following questions should be addressed before prescribing any antimalarial drug:

a. Will the traveler be exposed to malaria?
b. Will the traveler be in a drug-resistant *P. falciparum* zone?
c. Will the traveler have prompt access to medical care (including blood smears prepared with sterile equipment and then properly interpreted) if symptoms of malaria were to occur?
d. Are there any contraindications to the use of a particular antimalarial drug?

An overview of antimalarial drug regimens based on drug-resistance zones is provided in **Figure 6.1** and **Table 6.3**. It is important to note that a number of travelers to low-risk areas, such as urban areas and tourist resorts of Southeast Asia, continue to be inappropriately

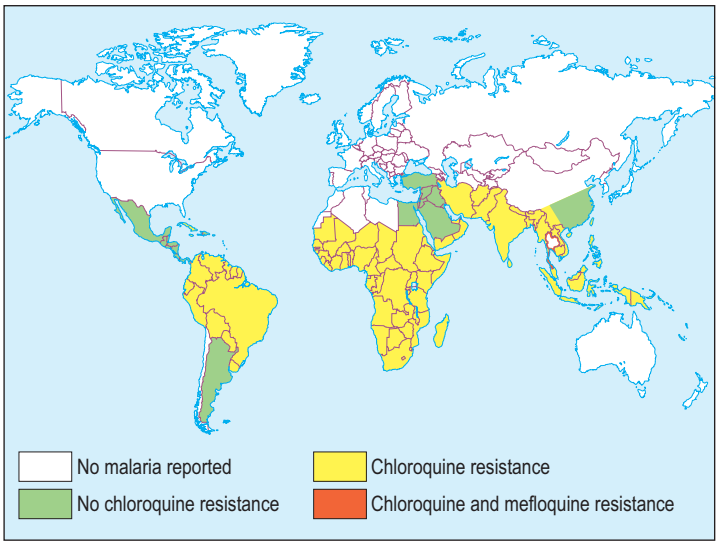

Fig. 6.1 Map of malaria-endemic areas and zones of drug-resistance. See Fig. 6.2 for detail. *Note*: This is meant as a *visual aid only*. The reader is referred to additional important details of malaria drugs and country-specific malaria risk available online (see Table 6.1) or in references. (From Health Canada. 2004. Canadian recommendations for the prevention and treatment of malaria among international travelers. CCDR 30S1.)

prescribed antimalarial drugs that result in unnecessary adverse events but offer little protection. Improved traveler adherence with antimalarial drugs is more likely when travel medicine practitioners make a concerted effort to identify and carefully counsel the high-risk traveler and avoid unnecessary drugs in the low-risk individual.

4. Seeking Early Diagnosis and Treatment If Fever Develops during or after Travel

Travelers should be informed that although personal protection measures and antimalarial drugs can markedly decrease the risk of contracting malaria, these interventions do not guarantee complete protection. Symptoms resulting from malaria may occur as early as 1 week after first exposure and as late as several years after leaving a malaria zone, whether or not chemoprophylaxis has been used. Most travelers who acquire falciparum malaria will develop symptoms within 2 months of exposure. Falciparum malaria can be effectively treated early in its course, but delays in therapy may result in a serious and even fatal outcome. The most important factors that determine outcome are early diagnosis and appropriate therapy. Travelers and healthcare providers alike must consider and urgently rule out malaria in any febrile illness that occurs during or after travel to a malaria-endemic area (see Chapters 20 and 21).

CURRENT CHEMOPROPHYLACTIC DRUG REGIMENS

Antimalarial drugs are selected based on individual risk assessment (as discussed previously) and drug-resistance patterns (**Figs. 6.1**, **6.2**, and **Tables 6.1**, **6.3**, and **6.4**). Chloroquine-resistant *P. falciparum* (CRPF) is now widespread in all malaria-endemic areas of the world, except for Mexico, the Caribbean, Central America, Argentina, and parts of the Middle

TABLE 6.3 Malaria Chemoprophylactic Regimens for At-Risk Individuals According to Zones of Drug-Resistance[a]

Zone	Drug(s) of Choice[b]	Alternatives
No chloroquine resistance	Chloroquine	Doxycycline or atovaquone-proguanil
Chloroquine resistance	Atovaquone-proguanil or doxycycline or mefloquine[c]	Primaquine[d]
Chloroquine and mefloquine resistance	Atovaquone-proguanil or doxycycline	
Adult doses		
Atovaquone-proguanil	One tablet daily	
Chloroquine phosphate	300 mg (base) weekly	
Doxycycline	100 mg daily	
Mefloquine	One tablet weekly (250 mg salt in the United States; base elsewhere)	
Primaquine	30 mg (base) daily[d]	

Note: Protection from mosquito bites (insecticide-treated bed nets, *N,N*-diethyl-meta-toluamide [DEET]-based insect repellents, etc.) is the first line of defense against malaria for all travelers. In the Americas and Southeast Asia, chemoprophylaxis is recommended only for travelers who will be exposed outdoors during evening or night time in rural areas.

[a]See detailed information in Table 6.4.

[b]Chloroquine and mefloquine are to be taken 1-3 weeks before entering malarial areas, continued during the stay in malarial areas, and taken for 4 weeks after leaving malarial areas. Doxycycline may be started 1 day before entering malarial areas but must be continued for 4 weeks after departure. Atovaquone-proguanil and primaquine are started 1 day before entering the malarial area and may be discontinued 7 days after leaving the malaria-endemic area.

[c]Adhere to boxed warning about contraindications before prescription.

[d]Contraindicated in glucose-6-phosphate dehydrogenase (G6PD) deficiency and during pregnancy. Not presently licensed for this use. Must perform the G6PD level test before prescribing.

East and China. *P. falciparum* malaria resistant to chloroquine and mefloquine is still rare except on the borders of Thailand with Cambodia and Myanmar (Burma). Resistance to sulfadoxine-pyrimethamine is now common in the Amazon basin and Southeast Asia and is increasing in many regions of Africa. Chloroquine-resistant *P. vivax* is also becoming an important problem, particularly in Papua New Guinea, Papua (formerly Irian Java), Vanuatu, Myanmar, and Guyana. More recently *P. knowlesi* has been indentified in Southeast Asia as causing clinical malaria resembling falciparum malaria.

Chloroquine-Sensitive Zones

Chloroquine is the drug of choice for travel to areas where chloroquine resistance has not been described. Chloroquine is active against the erythrocytic forms (**Fig. 6.3**) of sensitive strains of all species of malaria, and it is also gametocidal against *P. vivax*, *P. malariae*, and *P. ovale*. Except for its bitter taste, chloroquine is usually well tolerated and has a low incidence of serious adverse events. Dark-skinned persons may experience generalized pruritus that is not indicative of drug allergy. Retinal toxicity that may occur with long-term high doses of chloroquine used in the treatment of other diseases is extremely unlikely with chloroquine given as a weekly malaria chemosuppressive agent. Chloroquine use is suitable for people of all ages and for pregnant women. Because insufficient drug is excreted in breast milk to protect the infant, nursing infants should be given chloroquine. Contraindications include people who are glucose 6-phosphate dehydrogenase (G6PD) deficient or hypersensitive to 4-aminoquinoline compounds. Administration of the oral live typhoid vaccine and live cholera vaccine should be completed 3 days before chloroquine use, and chloroquine may suppress the antibody response to primary pre-exposure rabies vaccine.

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Fig. 6.2 Detail of Fig. 6.1 showing malaria-endemic areas and zones of drug resistance in Southeast Asia. *Note*: This is meant as a visual aid only. The reader is referred to additional important details of malaria drugs and country-specific malaria risk available online (see Table 6.1) or in references. (From Health Canada. 2004. Canadian recommendations for the prevention and treatment of malaria among international travelers. CCDR 3051.)

TABLE 6.4 Antimalarial Drugs, Doses,[a] and Adverse Effects (Listed Alphabetically)

Generic Name	Packaging	Adult Dose	Pediatric Dose	Adverse Effects
Artemether/ Lumefantrin	20 mg Artemether and 120 mg Lumefantrine in 1 tablet	Prevention: not indicated Treatment: 80 mg/480 mg (=4 Tbl.) initially, after 8 hours: 4 Tbl., then twice daily 4 Tbl. On day 2 and 3 (total = 24 Tbl.)	Prevention: not indicated Treatment: Licensed from 5 kg body weight. Total treatment: 6 doses (initially, then after 8, 24, 36, 48, and 60 hours) 5- <15 kg: 1 tablet/dose 15- <25 kg: 2 tablets/dose 25- < 35 kg: 3 tablets/dose ≥ 35 kg and >12 years: 4 tablets/dose	Frequent: GI symptoms, headache, dizziness Rare: QTs prolongation, cardiac arrhythmia, hemolysis
Atovaquone-proguanil	250 mg atovaquone and 100 mg proguanil (adult tablet)	Prevention: 1 tablet daily Treatment: 1000 mg atovaquone and 400 mg proguanil (4 tablets) once daily ×3 days	Prevention: 11-20 kg 1/4 tablet; 21-30 kg 1/2 tablet; 31-40 kg 3/4 tablet; >40 kg 1 tablet; (see Chapter 12 for AP pediatric tablet dosing schedule) Treatment: 20 mg/kg atovaquone and 8 mg/kg proguanil once daily ×3 days	Frequent: nausea, vomiting, abdominal pain, diarrhea, increased transaminases Rare: seizures, rash

Continued

TABLE 6.4 Antimalarial Drugs, Doses,[a] and Adverse Effects (Listed Alphabetically)—cont'd

Generic Name	Packaging	Adult Dose	Pediatric Dose	Adverse Effects
Chloroquine[b] phosphate	150 mg base	Prevention: 300 mg base once weekly Treatment: 1.5 g base ×3 days[c]	Prevention: 5 mg base once weekly 5-6 kg or <4 months: 25 mg base 7-10 kg or 4-11 months: 50 mg base 11-14 kg or 1-2 years: 75 mg base 15-18 kg or 3-4 years: 100 mg base 19-24 kg or 5-7 years: 125 mg base 25-35 kg or 8-10 years: 200 mg base 36-50 kg or 11-13 years: 250 mg base 50 kg or 14 years: 300 mg base Treatment: 25 mg salt/kg total over 3 days	Frequent: pruritus in black-skinned individuals, nausea, headache Occasional: skin eruptions, reversible corneal opacity Rare: nail and mucous membrane discoloration, nerve deafness, photophobia, myopathy, retinopathy with daily use, blood dyscrasias, psychosis and seizures, alopecia
Doxycycline[d]	100 mg	Prevention: 100 mg once daily Treatment: 1 tablet twice daily for 7 days (plus quinine) (see Chapter 20)	Prevention: 1.5 mg salt/kg once daily (max. 100 mg daily) <25 kg or <8 years: contraindicated 25-35 kg or 8-10 years: 50 mg 36-50 kg or 11-13 years: 75 mg ≥50 kg or ≥14 years: 100 mg Treatment: 1.5 mg salt/kg twice daily (max. 200 mg daily) <25 kg or <8 years: contraindicated 25-35 kg or 8-10 years: 50 mg twice daily 36-50 kg or 11-13 years: 75 mg twice daily 50 kg or ≥14 years: 100 mg twice daily (plus quinine) (see Chapter 20)	Frequent: GI upset, vaginal candidiasis, photosensitivity Rare: allergic reactions, blood dyscrasias, azotemia in renal diseases, hepatitis

Mefloquine	250 mg base	Prevention: 250 mg base once weekly Treatment: see text	Prevention: <5 kg: no data 5-9 kg: 1/8 tablet 10-19 kg: 1/4 tablet 20-30 kg: 1/2 tablet 30-45 kg: 3/4 tablet >45 kg: 1 tablet once weekly Treatment: see text	Common: transient dizziness diarrhea, nausea, vivid dreams, nightmares, irritability, mood alterations, headache, insomnia Rare: seizures, psychosis, prolonged dizziness
Quinine	330 mg salt	Prevention: not indicated Treatment: see text	Prevention: not indicated Treatment: see text	Common: cinchonism
Primaquine (*Note*: Must perform G6PD testing before use)	15 mg base	Prevention: prophylaxis: 30 mg base daily (see text) Terminal prophylaxis or radical cure: 30 mg base/day for 14 days[e]	Prevention: 0.5 mg base/kg daily Terminal prophylaxis or radical cure: 0.5 mg base/kg per day ×14 days[f]	Occasional: GI upset, hemolysis in G6PD deficiency, methemoglobinemia

G6PD, Glucose 6-phosphate dehydrogenase; *GI*, gastrointestinal.
[a]Dose for chemoprophylaxis, unless specified for "Treatment."
[b]Chloroquine sulfate (Nivaquine) is not available in the United States and Canada but is available in most malaria-endemic countries in both tablet and syrup form.
[c]Generally, 2 tablets twice per day on days 1 and 2, then 2 tablets on day 3 (total of 10 tablets).
[d]For treatment only in combination with other antimalarials.
[e]Doses increased to 30 mg base/day due to primaquine-resistant/tolerant *P. vivax*.
[f]Doses increased to 0.5 mg base/kg/day due to primaquine-resistant/tolerant *P. vivax*.

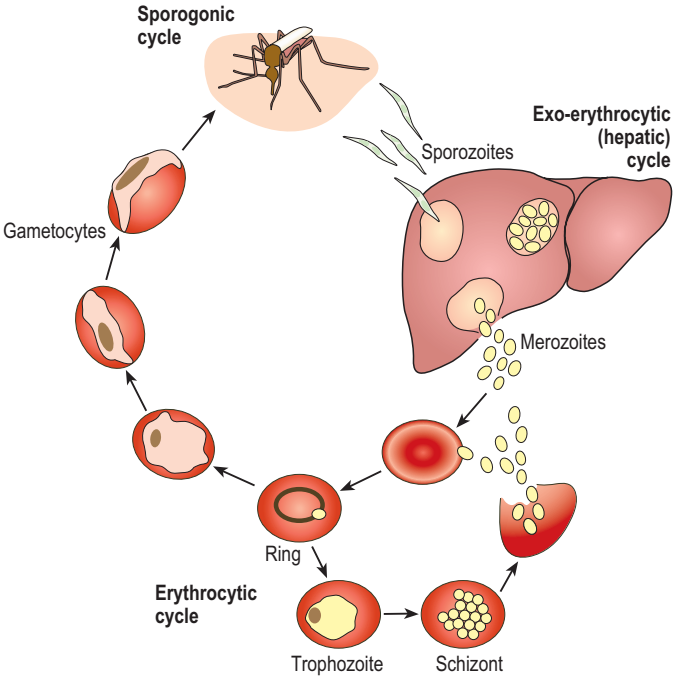

Fig. 6.3 Life cycle of the malaria parasite in humans. (Courtesy of Dr. Lena Serghides. Adapted from Serghides L., et al. 2005. CD36 and malaria: friend or foes? Trends Parasitol. 19(10):461–469.)

Chloroquine-Resistant Zones

For many travelers to these areas, a choice between atovaquone-proguanil (AP) (e.g., Malarone™), doxycycline (e.g., Vibramycin™), or mefloquine (e.g., Lariam™), will have to be made. Less commonly primaquine may be used. Deciding which agent is best requires an individual assessment of risk of malaria and the specific advantages and disadvantages of each regimen (**Table 6.5**). For drugs such as mefloquine and doxycycline to be optimally effective, they need to be taken for 4 weeks after leaving a malaria-endemic area, although traveler adherence with this component has been traditionally poor. Agents such as AP and primaquine are called causal prophylactics because they kill malaria early in its life cycle in the liver, and therefore may be discontinued 1 week after leaving an endemic area (**Fig. 6.3**). This advantage makes these drugs attractive for high-risk but short-duration travel. It is important to note that none of these agents is ideal, and all carry a risk of adverse events that are distressing enough to travelers that 1-7% will discontinue their prescribed chemoprophylactic regimen.

Atovaquone Plus Proguanil (Malarone)

Malarone is a fixed-dose combination of atovaquone and proguanil hydrochloride. AP works against the erythrocytic stages of all the *Plasmodium* parasites and the liver-stage (causal prophylaxis) of *P. falciparum*. The AP combination is effective against *P. falciparum* malaria strains that are resistant to a variety of other antimalarial drugs.

TABLE 6.5 Clinical Utility Score for Current Malaria Chemoprophylactic Regimens

Drug	Efficacy[a]	Tolerance[b]	Convenience[c]	Causal[d]	Cost[e]	Total
Atovaquone-proguanil	3	3	2	2	1	11
Doxycycline	3	2	2	0	3	10
Mefloquine	3	1	3	0	2	9
Primaquine	2	2	1[f]	2	3	10

Note: Scores and weighting are arbitrary and can be modified/individualized to specific travelers and itineraries.
[a]Efficacy: 1, <75%; 2, 75-89%; 3, ≥90%.
[b]Tolerance: 1, occasional disabling side effects; 2, rare disabling side effects; 3, rare minor side effects.
[c]Convenience: 1, daily and weekly dosing required; 2, daily dosing required; 3, weekly dosing required.
[d]Causal: 0, no causal activity; 2, causal prophylactic (may be discontinued within a few days of leaving risk area).
[e]Cost: 1, >US$100/month; 2, US$50-100/month; 3, <US$50/month.
[f]Requires a pre-travel G6PD measurement, resulting in a lower convenience score.

Atovaquone inhibits parasite mitochondrial electron transport at the level of the cytochrome bc1 complex and collapses mitochondrial membrane potential. The plasmodial electron transport system is 1000-fold more sensitive to atovaquone than the mammalian electron transport system, which likely explains the selective action and limited side effects of this drug. Proguanil is metabolized to cycloguanil, which inhibits dihydrofolate reductase and impedes the synthesis of folate cofactors required for parasite DNA synthesis. AP works synergistically since proguanil, which alone has no effect on mitochondrial membrane potential or electron transport, significantly enhances the ability of atovaquone to collapse mitochondrial membrane potential; however, this is not mediated through the cycloguanil metabolite. This might explain why proguanil enhances atovaquone activity even in the presence of documented cycloguanil resistance or in patients deficient in the cytochrome P450 enzymes required for the conversion of proguanil to cycloguanil.

In randomized, controlled trials, AP was highly efficacious in preventing *P. falciparum* malaria in both adults and children. Four published trials have examined the protective efficacy of AP in semi-immune adults and children living in malaria-endemic areas. The overall efficacy of AP in the prevention of *P. falciparum* malaria in these trials was 98% (95% CI 91.9-99.9%). The protective efficacy of AP for prevention of *P. falciparum* malaria in non-immune adults and children has been examined in five clinical trials, four of which were randomized, and three blind. Collectively, the protective efficacy of AP was 96-100% (95% CI 48-100%). Only one randomized, double-blind, placebo-controlled trial has evaluated the protective efficacy of AP against *P. vivax*. The protective efficacy of AP was 84% (95% CI 45-95%) for *P. vivax* and 96% (95% CI 71-99%) for *P. falciparum*. As AP does not appear to eradicate *P. vivax* hypnozoites, it is suggested that travelers to areas where the transmission rates of *P. vivax* are high should receive consideration for presumptive antirelapse therapy with primaquine.

Controlled trials indicate that AP at prophylactic doses is well tolerated by adults and children with drug discontinuation rates of 0-2%. The most commonly reported adverse events are headache and abdominal pain (which can often be reduced by taking AP with food); however, in placebo-controlled trials, these occurred at similar rates as in placebo recipients. In two large randomized, double-blind clinical trials in non-immune subjects traveling to a malaria-endemic area, chemoprophylactic drugs were well tolerated, but AP was significantly better tolerated than either mefloquine or chloroquine/proguanil (CP) in these studies. Participants receiving AP reported significantly lower rates of neuropsychiatric adverse events (14% vs. 29%) compared with mefloquine, significantly lower gastrointestinal adverse events (12% vs. 20%) compared with CP, and lower drug discontinuation rates compared with both. In another randomized trial in travelers, AP was the best-tolerated

chemoprophylactic with discontinuation rates of 1.8% versus 3.9% for mefloquine and doxycycline and 5.2% for CP. Additionally, efficacy and tolerability have been examined in pediatric travelers using a randomized comparative trial of AP versus CP. There were no prophylactic failures, but AP was better tolerated with no premature discontinuation of AP due to an adverse event, compared with a 2% discontinuation rate with CP.

AP is currently indicated for the prophylaxis and treatment of *P. falciparum* malaria including areas where chloroquine and/or mefloquine resistance has been reported. Travelers who have experienced intense exposure to *P. vivax* and *P. ovale* should be considered for radical treatment with primaquine on leaving the malaria-endemic area. Because of its causal activity, AP is taken 1 day prior to travel in a malarious zone, daily while exposed, and for 7 days on leaving.

AP is contraindicated in those with severe renal impairment and in those with a history of hypersensitivity to any of the drug components. AP is currently approved for the prevention of malaria in children >5 kg and adults in the United States, Australia, and Europe. A lack of data exists for the use of AP during pregnancy or breast feeding, and it is not currently recommended for chemoprophylaxis. Although a recent but small study suggests that AP is safe and well tolerated in pregnancy, additional data are needed. AP should not be given with other proguanil-containing medications, or with tetracycline, rifampin, rifabutin, and metoclopramide, which significantly reduce the plasma concentration of atovaquone.

Doxycycline

Doxycycline is a relatively slow-acting schizonticidal agent and, while not appropriate on its own for treatment, is efficacious as a solo chemoprophylactic agent against drug-resistant *P. vivax* and *P. falciparum* malaria.

A number of randomized trials have examined the efficacy of doxycycline as a chemoprophylactic in non-immune and semi-immune populations. The reported protective efficacy in these trials was excellent, ranging from 92 to 100% against *P. falciparum* and *P. vivax*. In comparative trials in areas with chloroquine-resistant *P. falciparum* malaria, doxycycline has been shown to be equivalent to mefloquine and AP and superior to azithromycin and chloroquine-proguanil. Parasite resistance to doxycycline has not been reported to be an operational problem in any malaria-endemic area thus far. Poor adherence to daily use rather than true drug resistance is the major reason for doxycycline failures.

Overall, a number of comparative studies have shown that doxycycline is well tolerated as a chemoprophylactic agent and has relatively few reported side effects. In clinical trials, doxycycline was tolerated as well as or better than placebo or the comparator drug, with few serious adverse events reported. The most commonly reported adverse events related to doxycycline use are nausea, vomiting, abdominal pain, and diarrhea. Esophageal ulceration is a rare but well-described adverse event associated with doxycycline use. Taking doxycycline with food and plentiful fluids and remaining in an upright position for ≥1 hour can reduce adverse gastrointestinal effects. Dermatologic reactions, including photosensitivity, are also adverse events frequently associated with doxycycline use. Although doxycycline has a lesser effect on normal bacterial flora than other tetracyclines, it still increases the risk of oral and vaginal candidiasis in predisposed individuals.

Doxycycline is currently indicated as an agent of choice for prevention of mefloquine-resistant *P. falciparum* malaria or an alternative to AP or mefloquine for the prevention of CRPF malaria. Doxycycline should be taken once daily, beginning 1-2 days before entering a malarious area, and should be continued while there. Because of its poor causal effect, it must be continued for 4 weeks after leaving the risk area. Doxycycline is contraindicated during pregnancy, in breast-feeding women, and in children <8 years old, and should not be taken within 1-3 hours of administering Bismuth subsalicylate, an oral antacid, or iron. Long-term safety (>3 months) of daily doxycycline use has not been established among travelers, but chronic use of related tetracyclines by young healthy adults in acne treatment protocols is a common clinical practice.

Mefloquine

Mefloquine is a potent, long-acting blood schizontocide (**Fig. 6.3**) and has >90% protective efficacy against all malarial species including *P. falciparum* resistant to chloroquine and pyrimethamine-sulfonamide combinations. The CDC and WHO list mefloquine as one of the drugs of choice for high-risk travelers to chloroquine-resistant regions such as sub-Saharan Africa and New Guinea. Mefloquine is effective in the prevention of CRPF malaria, except for rural Thai border regions with Myanmar and Cambodia, where parasites display multidrug resistance, including to mefloquine. Although there is general agreement about the drug's efficacy, the drug tolerance has been called into question. Approximately 25-50% of mefloquine users report side effects, the majority of which are mild and self-limited. The most frequent adverse events reported by mefloquine users are nausea, strange dreams, dizziness, mood changes, insomnia, headache, and diarrhea. Severe neuropsychiatric reactions (psychosis, convulsions) are infrequent with prophylactic doses and are reported to occur in approximately 1/6000 to 1/13,000 individuals. Less severe but nonetheless troublesome neuropsychologic adverse events (e.g., anxiety, depression, nightmares) disabling enough to result in drug discontinuation are reported in 0.2-3.9% of users. There is no evidence that the long-term use of mefloquine (>1 year) is associated with additional adverse effects.

Data from well-designed prospective and randomized trials show that, for the most part, mefloquine is well tolerated. Overall mefloquine withdrawal rates in comparative trials were estimated to be 1-5%, indicating high acceptance rates comparable to other chemoprophylactic regimens and suggesting that <5% of individuals would need to switch to an alternative drug regimen. In randomized controlled trials comparing mefloquine with AP or doxycycline in non-immune travelers, all agents were effective and well tolerated, but AP and doxycycline were significantly better tolerated.

Contraindications to the use of mefloquine include a history of psychiatric illness including anxiety and depression, seizure disorder, and a history of hypersensitivity to mefloquine or related substances including quinine. Precautions include its use in children weighing <10 pounds, cardiac conduction disturbances or arrhythmia, and the concurrent use of quinine-like drugs (e.g., halofantrine and mefloquine should not be used together). In 2013 the Food and Drug Administration (FDA) and European Medicines Agency (EMA) issued a boxed warning on contraindications before the prescription of mefloquine and made it mandatory that a mefloquine user should carry a wallet pass.

The manufacturers of mefloquine also caution about its use by drivers, pilots, and machine operators because of concerns that it may affect spatial orientation and motor coordination. There are no data on mefloquine use by scuba divers; however, caution is advised because of the risk of neurologic symptoms developing at depth and because signs and symptoms of decompression illness (dizziness, headache, nausea, fatigue) may be attributed to the drug, thus potentially delaying recognition and appropriate treatment for the decompression problem. Mefloquine is metabolized through the liver, so should be avoided in travelers with chronic hepatic dysfunction, and can also cause an asymptomatic increase in the liver function tests during therapy. Travelers on drugs such as warfarin or cyclosporin A should start mefloquine 3-4 weeks in advance of departure, so that prothrombin times or cyclosporine A levels can be monitored and adjusted as needed.

For a traveler to a CRPF destination who plans to engage in special physical activities, such as those mentioned previously, and who cannot take AP or doxycycline (see later discussion), a practical approach would be to start the traveler on mefloquine approximately 3 weeks before departure and monitor for adverse events. It has been suggested by many travelers that if the drug is taken in the evening, side effects are mostly relegated to the hours of sleep and effects on physical performance the next day are potentially lessened.

Travelers who will be at immediate high risk of drug-resistant falciparum malaria may be given a loading dose of mefloquine. Data from several trials indicate that mefloquine taken once a day for 3 days before travel followed by standard weekly doses is an effective way to rapidly achieve therapeutic blood levels (in 4 days compared with 7-9 weeks with standard weekly dosing of mefloquine). Approximately 2-3% of loading-dose recipients

discontinued mefloquine (most commonly for gastrointestinal upset and dizziness), and most of these did so during the first week. Alternatively, mefloquine can be initiated 2-3 weeks before travel to achieve higher blood levels before entering malaria-endemic areas. Either strategy permits an assessment of drug tolerance before travel and allows a change to a suitable alternative if required.

Primaquine

Primaquine is an 8-aminoquinoline that has antimalarial activity against both blood and tissue stages and can be used as a chemoprophylactic agent as well as for "terminal" prophylaxis. Recent randomized controlled field trials have convincingly demonstrated the prophylactic potential of primaquine, showing a protective efficacy of 85-95% against both *P. falciparum* and *P. vivax* infections.

Primaquine has been shown to be tolerated as well as or better than other standard regimens but may cause nausea and abdominal pain that can be decreased by taking the drug with food. Of importance, primaquine may cause oxidant-induced hemolytic anemia with methemoglobinemia, particularly in individuals with a deficiency of G6PD. It is contraindicated in patients with G6PD deficiency and also during pregnancy. If not already documented, a traveler's G6PD status should be determined with a G6PD blood test before primaquine is prescribed. The use of primaquine as a malaria chemoprophylaxis regimen during travel is off-label (FDA, April, 2015). However, in the absence of contraindications, primaquine may be a useful alternative prophylactic agent to consider for selected travelers, and because of its causal acitvity may be discontinued 1 week after leaving an endemic area.

If the risk of *P. vivax* infection is thought to be particularly high (e.g., in long-term expatriates and soldiers) a 14-day course of primaquine phosphate ("radical" or "terminal" prophylaxis, also called presumptive antirelapse therapy) may be given at the conclusion of the standard post-travel chemoprophylaxis regimen to eliminate latent hepatic parasites (as indicated by the FDA label). See section below, Primaquine for Relapse Prevention.

Chloroquine and Mefloquine-Resistant Zones

For evening and overnight exposure in rural regions along the Thai-Myanmar and Thai-Cambodian border, doxycycline or AP are the drugs of choice.

Contrasts in Prophylaxis Recommendations among Health Organizations

As mentioned above, the major health organizations including the CDC, Health Canada, the UK Foreign and Commonwealth Office (FCO), and the WHO all have detailed information available on their websites about malaria chemoprophylaxis and areas of drug resistance, by country (**Table 6.1**). It should be noted that these sites are constantly being updated and need to be updated and checked frequently. Areas of controversy between different advisory groups include the Indian subcontinent, Latin America, and parts of southern Africa, including South Africa, Namibia, and Botswana, where despite studies showing significant chloroquine resistance, some groups still continue to recommend chloroquine or chloroquine combinations.

Frequent Short-Term Travel to High-Risk Areas

If travelers are expecting to take several short trips over a period of months to areas of high malarial transmission, the use of causal antimalarials such as AP and primaquine should be strongly considered. Since standard chemoprophylactic drugs such as doxycycline and mefloquine require use for 4 weeks after malaria exposure, travelers in this situation would be constantly on antimalarials for many months. Causal drugs, due to their activity on the parasite liver stages, need to be taken only for a short time (1 week) after leaving the malaria-endemic area and are more user-friendly for this type of travel. Examples might include living in Bangkok (no malaria risk) but with frequent travel to rural areas of Laos or Cambodia for a few days each month. A similar situation exists in Nairobi, Kenya (one of few malaria-free areas in East Africa), where travel outside the city places individuals at risk of chloroquine-resistant *P. falciparum* malaria.

Summary

In summary, the use of antimalarials for chemoprophylaxis should be carefully directed at high-risk travelers where their benefit most clearly outweighs the risk of adverse events. None of the available regimens is ideal for all travelers, and the travel medicine practitioner should attempt to match the individual's risk of exposure to malaria to the appropriate regimen based on drug efficacy, tolerance, and safety. As a guide to facilitate decision making, we have generated a Clinical Utility Score, in which different attributes of each drug regimen, such as efficacy, tolerance, convenience, and cost, are weighted based on clinical trials and experience with these drugs (**Table 6.5**). The scores assigned are arbitrary, and other groups and users may weight each variable somewhat differently depending on the specific needs and risk of drug-resistant malaria. For example, a traveler to rural Papua may weigh efficacy more heavily than cost or convenience.

Dosing regimens may affect the traveler's acceptance of and compliance with the regimen prescribed. Chloroquine and mefloquine are taken once weekly beginning 1-3 weeks before travel, during travel, and for 4 weeks after leaving the endemic area. Doxycycline is taken once a day beginning 1-2 days before travel, during travel, and for 4 weeks after leaving an endemic area. The fixed dose combination drug AP (atovaquone plus proguanil) is taken once a day beginning 1-2 days before travel and every day during travel; because AP is active against liver stages of malaria, it can be discontinued 1 week after leaving an endemic area.

OTHER DRUGS

Drug Regimens to Avoid for Chemoprophylaxis

Amodiaquine

Amodiaquine, a drug that is structurally similar to chloroquine, is not recommended for use as a chemoprophylactic agent, although it is still used for therapy in parts of sub-Saharan Africa. Potential severe adverse events include agranulocytosis and hepatitis.

Artemisinin Derivatives, Alone or in Combination with Other Antimalarials

Artemisinin derivatives, including Artesunate, either alone or in combination with other malaria drugs such as lumefantrine, are a class of extremely effective therapeutic agents; however, there is currently no role for these drugs in malaria chemoprophylaxis.

Chloroquine plus Proguanil

An older alternative for travelers with contraindications or intolerance to mefloquine, AP, or doxycycline is the combination of weekly chloroquine plus daily proguanil. This combination is no longer recommended in the United States, Canada, and many countries of Europe to prevent malaria due to high levels of resistance in many malaria-endemic areas. Proguanil is not available in the United States but is available in Canada, Europe, and many malaria-endemic countries. The combination of proguanil and chloroquine is considered safe during pregnancy. Reported side effects of proguanil include mouth ulcerations, gastrointestinal upset, and hair loss. The gastrointestinal side effects may be lessened by taking the drugs with meals. Chloroquine plus proguanil is more efficacious in sub-Saharan Africa than chloroquine alone, but it is considerably less efficacious than doxycycline, mefloquine, or AP. Many failures have been reported in travelers taking this combination, and users must be informed that they are taking a less efficacious regimen.

Halofantrine

Halofantrine continues to be used in some countries as a therapeutic agent for malaria; however, it is not recommended for the prevention or treatment of malaria due to its potential to cause potentially fatal cardiac arrhythmias and prolongation of the QTc intervals, which can be accentuated when used in combination with other antimalarials that can affect cardiac conduction such as mefloquine.

Pyrimethamine plus Sulfadoxine (Fansidar)

This drug combination interferes with folic acid metabolism in the parasite: pyrimethamine inhibits dihydrofolate reductase, and sulfadoxine inhibits dihydropteroate synthetase. Fansidar was used as a weekly chemoprophylactic regimen against CRPF malaria in the 1980s, but an unacceptable rate of serious and sometimes fatal hypersensitivity reactions that developed during therapy with the weekly dose resulted in withdrawal of the recommendation for its use in prophylaxis. At present, Fansidar is still used for treatment in Africa.

Pyrimethamine plus Dapsone

This drug combination is marketed as Maloprim in many malaria-endemic areas outside the United States and, like Fansidar, interferes with folic acid metabolism in the parasite. This drug combination is not as efficacious as mefloquine, AP, or doxycycline in preventing malaria. However, the tablets containing the fixed-dose combination are relatively inexpensive and often sold over the counter in foreign countries; thus travelers have been known to start taking this drug during travel in lieu of more efficacious antimalarial drugs, on the advice of other travelers or local pharmacies. Travelers should be told to avoid Maloprim and should be educated about the possible and potentially serious dose-related toxicity (bone marrow suppression) of this drug combination.

Quinine

While quinine remains a first-line therapeutic agent for CRPF malaria, it is not used as a prophylactic drug due to its short half-life and its frequent treatment-associated adverse effects, including nausea, vomiting, headache, tinnitus, cardiovascular toxicity, and risk of blackwater fever with prolonged use.

STANDBY EMERGENCY MALARIA THERAPY (SBET)

Most travelers will be able to obtain prompt medical attention when malaria is suspected and therefore will not require a self-treatment regimen. Under unusual circumstances individuals at risk of malaria may be unable to seek medical care within 24 hours and may require self-treatment for presumptive malaria. However, because of the nonspecific symptoms of malaria, the potentially serious risk of incorrectly treating another disease, and the potential toxicity of malaria therapy, self-treatment should never be undertaken lightly; consultation with a tropical medicine expert is recommended before individuals are placed on self-treatment protocols. Travelers should be advised that the clinical presentation of malaria is variable and may mimic other diseases. An alternate diagnosis that requires treatment may be present, particularly in travelers who have been compliant with chemoprophylaxis. The most frequent symptoms of malaria are fever, headache, and generalized aches and pains. Fever, which may or may not be cyclical, is almost always present. Malaria can be misdiagnosed as "influenza" or another febrile illness, so that an early and accurate diagnosis is essential. Travelers for whom self-treatment has been recommended should be told that self-treatment is not considered definitive treatment but is a temporary, life-saving measure until they can receive medical attention. Self-treatment for malaria should be used only if travelers develop fever and professional medical care is not available within 24 hours. After self-treatment, medical attention should still be sought as soon as possible.

Rapid detection of malaria using immunochromatographic or dipstick tests may be available to some travelers. The sensitivity and specificity of these tests in research labs appears promising (>90%). However, the accuracy of these tests is not known in the hands of inexperienced operators and with ambient temperatures in the tropics. A summary of self-treatment regimens is presented in **Table 6.6**. Below is summarized important information about SBET regimens and those to avoid. Note that individuals who are on chemosuppression should never attempt treatment with the same drug, as there is the potential for additive toxicity and reduced efficacy.

TABLE 6.6 Self-Treatment Regimens[a]

A. For individuals in chloroquine-sensitive regions and not on chloroquine prophylaxis: self-treatment with chloroquine should be taken (Table 6.4). Seek medical help as soon as possible. Chloroquine prophylaxis should be started.

B. For individuals in chloroquine-sensitive regions and already on chloroquine prophylaxis: self-treatment with atovaquone-proguanil should be taken (Table 6.4). Seek medical help as soon as possible. Chloroquine prophylaxis should be resumed.

C. In chloroquine or chloroquine- and mefloquine-resistant *P. falciparum* regions, treatment recommendations for uncomplicated *P. falciparum* include the following (Table 6.4): begin oral atovaquone-proguanil (Table 6.4). Seek medical help as soon as possible. Appropriate prophylaxis should be resumed.

OR

Begin oral Artemether/Lumefantrine (Table 6.4). Seek medical help as soon as possible. Appropriate prophylaxis should be resumed.

[a]*Note*: To be used only if fever develops and medical care is not available within 24 hours. Self-treatment is not routine and in the United States and Canada is considered only for certain travelers and certain circumstances. If vomiting occurs within 30-60 minutes of dose, repeat full dose. If vomiting occurs 1-2 hours after dose, repeat one-half dose.

Atovaquone plus Proguanil (Malarone™)

Atovaquone-proguanil (AP; see the previous discussion) is an attractive agent for emergency self-treatment, provided the traveler is not taking this agent for prophylaxis. Apart from occasional gastrointestinal intolerance (reduced by taking the drug with food), treatment doses of AP are well tolerated (adult dose, 4 tablets/day for 3 days). It is safe for children (>10 pounds), but its safety in pregnancy and during breast feeding are unknown, and until additional data are available it should be avoided in these situations (see Chapter 14).

Artemether/Lumefantrin (Coartem™, Riamet™)

Coartemether (Riamet™ in Europe, Coartem in Africa and the United States) is a combination of artemether and lumefantrine. Coartemether is licensed in most European countries, Australia, and the United States for the treatment of uncomplicated malaria in adults and children >10 pounds and is becoming widely distributed in Africa. A six-dose regimen of artemether-lumefantrine appears more effective than antimalarial regimens not containing artemisinin derivatives.

Coartemether is generally well tolerated. Reported adverse effects are mostly gastrointestinal upset, headache, and dizziness. Coartemether is contraindicated for patients with a family history of sudden heart death or prolongation of the QTc interval. Also contraindicated is the concomitant use of drugs that might prolong the QTc interval and induce CYP3A4 (e.g., erythromycin, ketoconazole, rifampicine, carbamazepine, phenytoin, and St. John's wort).

The safety of artemisinin derivatives in pregnancy has not been established.

SPECIAL THERAPEUTIC CONSIDERATIONS

The Pregnant Traveler

Falciparum malaria in a pregnant woman poses significant risks for the mother, fetus, and the neonate. *P. falciparum* infection during pregnancy increases the risk of spontaneous abortion and stillbirth, intrauterine growth retardation, premature delivery, and maternal mortality. Travel by pregnant women or women who might become pregnant to destinations where CRPF malaria is transmitted should be avoided or deferred when possible. This advice is based on the fact that most effective antimalarial regimens against CRPF are neither recommended nor adequately studied during pregnancy, especially in the first trimester.

If a pregnant woman must travel to a CRPF malaria-endemic area, the use of insect repellents and treated bed nets (see Chapter 1) should be strongly encouraged. If the travel is to an area where there is intense transmission of CRPF with high-grade chloroquine resistance and travel cannot be deferred, mefloquine may be considered for chemoprophylaxis. For areas with less intense transmission, some experts recommend that chloroquine and proguanil chemoprophylaxis can be considered, although its efficacy is certainly limited. Some sources recommend dietary supplementation with folic acid for pregnant women taking proguanil.

At present there are insufficient data available on the use of AP in pregnancy or breast feeding, and therefore it is not recommended unless the potential benefit outweighs the potential risk to the fetus. Doxycycline is contraindicated in pregnancy and breast feeding. Conception should be delayed until 1 week after completion of doxycycline. Primaquine is contraindicated in pregnancy though is considered safe in breast feeding provided that the infant and mother are both screened for G6PD deficiency. There is currently no safe and effective chemoprophylaxis regimen for pregnant women at risk of mefloquine-resistant *P. falciparum* malaria.

The Infant Traveler

Malaria chemoprophylaxis in the very young infant is difficult to achieve. Although most antimalarial drugs taken by the mother will be present in breast milk, drug concentrations are not considered high enough to provide an adequate protective dose to the nursing infant. Thus malaria prevention in the nursing infant must be addressed separately from what is recommended to the mother.

For pediatric travelers to malarious areas where chloroquine is still effective, the chloroquine dose can be adjusted based on weight (**Table 6.4**). Chloroquine phosphate pediatric suspension is available in some destination countries, but not in the United States or Canada. If the suspension is not available, chloroquine phosphate tablets (250 mg salt = 150 mg chloroquine base) can be ground up by the pharmacist, and the weight-adjusted dose plus a filler can be put into capsules. Once a week, the capsule can be opened and the chloroquine powder mixed into a syrup to be given to a child. Chocolate syrup is recommended over fruit syrups and jams, as chocolate can effectively mask the extremely bitter taste of the chloroquine and make the mixture palatable to a child.

AP (Malarone) (available in a one-quarter-strength pediatric tablet) and mefloquine dosage for children can be adjusted based on weight for those weighing more than 10 pounds. Doxycycline is contraindicated in children <8 years old. In addition to chemoprophylaxis, the use of insect repellents formulated for pediatric use and insecticide-impregnated bed nets is recommended (see Chapters 1 and 12).

The Immunocompromised Traveler

P. falciparum malaria has been shown to increase HIV-1 replication and increase proviral loads and may cause faster progression of HIV-1 disease. HIV-1 infection also appears to make malaria worse and is associated with higher parasitemia infections and an increase in clinical malaria.

Another concern is antimalarial and antiretroviral drug interactions. Both mefloquine and protease inhibitors are metabolized by cytochrome P450. Inducers or inhibitors of cytochrome P450 might be expected to alter drug levels of these agents. Mefloquine has been shown to decrease the drug levels of ritonavir, but ritonavir had little effect on mefloquine. There is reported to be less interaction between mefloquine and other protease inhibitors such as nelfinavir or indinavir. There are few available data on the interaction of other antiretrovirals with mefloquine. Atovaquone increases the level of some nucleoside reverse transcriptase inhibitors, but whether this increases the risk of adverse drug events is unknown. There are also few data available regarding the potential interaction of proguanil and antiretroviral agents.

Doxycycline may cause photosensitivity, similar to antiretrovirals such as abacavir, and predispose to candidiasis, potential problems for HIV-infected individuals.

Because of potential or unknown interactions between antiretroviral and antimalarial drugs, it may be advantageous to start an antimalarial drug in advance of the recommended start date in order to monitor for any adverse effects.

As in other travelers, a CRPF malaria infection could result in a serious and life-threatening illness, so insect precautions and malaria chemoprophylaxis appropriate to the itinerary should be strongly encouraged. Travel advice for the HIV-infected traveler is discussed more fully in Chapter 15.

The Traveler without a Spleen

Overwhelming infection from encapsulated bacteria, such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis* (meningococcus) is a recognized risk in persons who have undergone splenectomy. Medical advisors have postulated that malaria also would be more difficult to control in the splenectomized host, since the spleen serves as a major site for removal of parasitized red cells from the circulation. A review of the clinical course and treatment of malaria in a group of splenectomized patients, although based on a limited number of observations, suggested that splenectomized patients were significantly more likely to have *P. falciparum* parasitemia and febrile symptoms than controls. Parasite densities reached significantly higher levels, and mature parasite stages were more often seen in the peripheral blood, in asplenic individuals.

Long-Term Travelers

Few data are available on efficacy and tolerability of long-term malaria chemoprophylaxis. The long-term traveler requires expert advice on malaria risk and seasonality and practical guidance regarding long-term use of medications, especially since adherence is an issue over long periods of travel or deployment. Mefloquine has been used successfully for up to 2.5 years and was shown to be well tolerated and effective in preventing falciparum malaria. Toxic accumulation does not occur during long-term intake. AP can be used for long-term travelers, and US and Canadian guidelines do not limit the period of prophylaxis, although there is a 28-day limit in some countries. Few data exist on the long-term (>6-month) use of doxycycline in malaria chemoprophylaxis. Insect protection measures such as insecticide-treated bed nets and effective insect repellents are an essential component of malaria protection for long-term travelers.

PRIMAQUINE FOR RELAPSE PREVENTION

Terminal chemoprophylaxis, "the radical cure," or presumptive antirelapse therapy, refers to treatment with primaquine phosphate, an antimalarial compound that can eradicate latent malaria (*P. vivax* or *P. ovale*) incubating in the liver. Currently, the standard adult regimen consists of primaquine phosphate at a dose of 30 mg base daily with food for 2 weeks. An alternative regimen consists of three tablets (45 mg base) once a week for 8 weeks (**Table 6.4**). Common side effects are nausea and malaise.

The risk of latent hepatic malaria infections causing attacks of relapsing malaria beyond the standard 4-week period of post-travel malaria chemoprophylaxis increases with the degree of exposure to mosquito bites in the malarious area. Although post-travel primaquine therapy is not routinely advised, travelers who spent prolonged periods in rural areas of malarious countries or who report an inordinate number of mosquito bites may be candidates for primaquine therapy.

Treatment with primaquine is usually initiated at the time of the last dose of post-travel chemoprophylaxis or the last dose of treatment for a malaria attack caused by *P. vivax* or *P. ovale*. Primaquine can cause severe hemolytic anemia in persons with red cells low in G6PD, which is more common in persons of African, Asian, or Mediterranean origin. G6PD testing should be used before initiation of primaquine therapy.

Primaquine-Resistant or Tolerant *P. vivax*

P. vivax strains that do not respond to the formerly used dosage regimen of primaquine (adults, 15 mg base/day) for terminal prophylaxis have been reported from Papua, Papua

New Guinea, India, South America, and Somalia. Since primaquine tolerance is widespread, most experts now recommend using 30 mg base/day for adults for all cases of *P. vivax* malaria (0.5 mg/kg in children), provided the individual has a normal G6PD level. Primaquine is associated with nausea and vomiting, which can be reduced by giving the drug with food.

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