

Treatment and Prevention of Malaria: An Update

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The impact of malaria on global health is staggering. With an estimated incidence of almost 300 million new cases each year, resulting in more than 1.5 million deaths annually worldwide, malaria remains a major global public health concern.¹ Along with tuberculosis and HIV infection, malaria forms a disease triad that accounts for almost half of all infectious disease mortality.

Although malaria acquired in the United States is rare, travelers to areas where malaria is endemic need to be aware of their risk for infection, and their physicians must consider the diagnosis of malaria for any febrile illness that occurs during or after travel to a malaria-endemic area. Most cases of fatal imported malaria occur because of failure to prescribe or comply with appropriate chemoprophylaxis or because of a delay in diagnosis.

This review will focus on recent developments in the prevention and treatment of malaria to heighten awareness among physicians about this important global parasitic infection.

EPIDEMIOLOGY

Over the last 2 decades, areas where malaria is endemic have witnessed both a deterioration in malaria control and a resurgence of cases because of the appearance and geographic spread of drug-resistant *Plasmodium falciparum* infection, population movement, deteriorating sanitation, and climatic changes. Two thirds of reported malaria cases originate in Africa, India, Sri Lanka, Vietnam, the Solomon Islands, Colombia, and Brazil.² Falciparum malaria has become a significant problem along the Amazon in Brazil, Guyana, Peru, and Bolivia. Chloroquine resistance has become widespread in all areas where malaria is endemic, with the exception of Mexico, Central America, the Caribbean, Argentina, China, and parts of the Middle East (Figure 1). Increasing drug resistance has been reported in the Indian subcontinent and in Thailand, especially along its borders with Cambodia and Myanmar.² The majority of deaths caused by falciparum malaria, however, continue to occur in sub-

Saharan Africa, primarily among children younger than 5 years and pregnant women living in remote rural areas with limited access to health services.

Coincident with the global resurgence in malaria, an increase in international travel to malaria-endemic areas has placed a growing number of travelers at risk for contracting the disease. It is currently estimated that between 10,000 and 30,000 travelers from industrialized countries contract malaria each year.² Since 1990, almost 5000 cases of imported malaria have been reported in US civilian travelers, the majority of whom were not on an appropriate regimen of chemoprophylaxis.³ During 1999, a total of 1540 cases were reported to the Centers for Disease Control and Prevention (CDC) among persons in the United States or its territories, an increase of 25.5% from the 1227 cases reported in 1998.⁴ Of this total, 833 cases occurred in US civilians, the highest number of cases in this group reported in the past 30 years (Figure 2).³ Total cases acquired in Africa rose 27.6% (n = 901) in 1999 compared with 1998, and cases acquired in Asia increased by 2.9% (n = 246). Cases from the Americas increased by 19.7% (n = 274) from 1998. Five deaths attributable to malaria in persons residing in the United States were reported in 1999.³

Rarely, malaria can be acquired in the United States. Residents of an area where malaria is not endemic who lack any history of blood transfusion, organ transplantation, or needle sharing presumably acquire malaria via local susceptible mosquitoes that have become infected after biting persons who had contracted the disease elsewhere. The source of these cryptic cases has generally been traced to unregistered migrant farm workers and recent immigrants from countries where malaria is endemic.⁵

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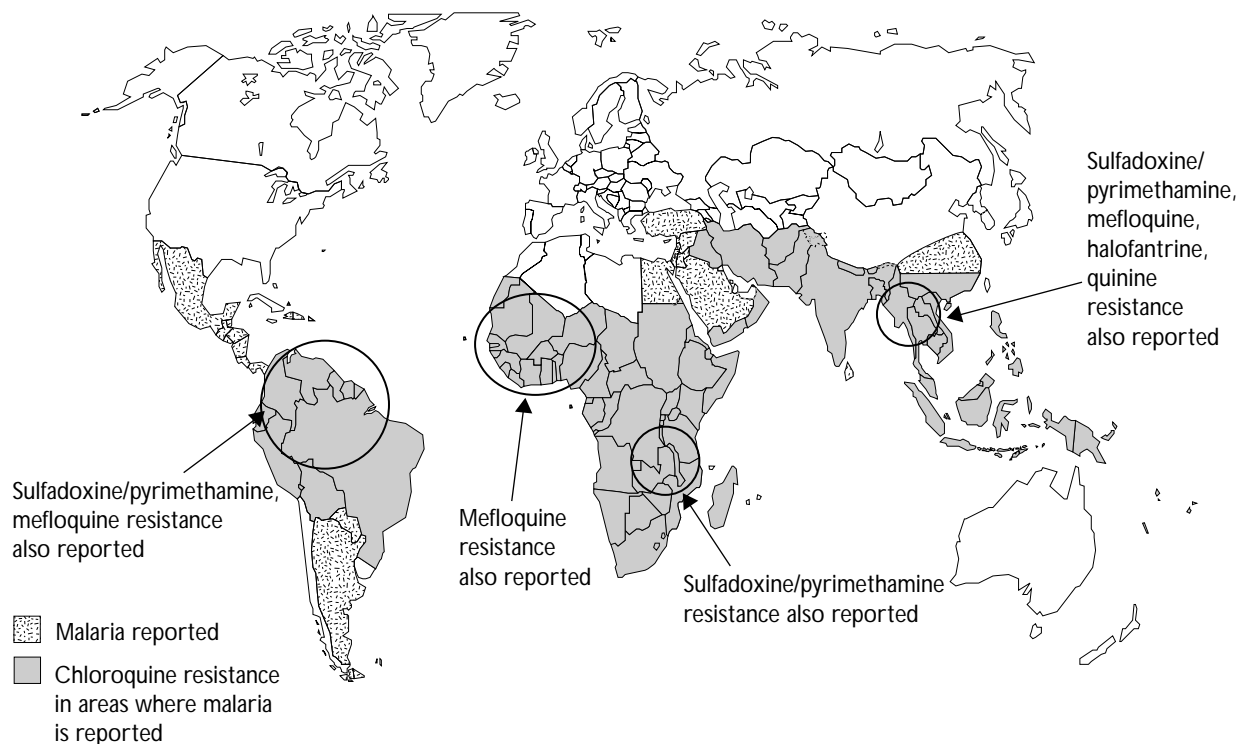


Figure 1. Resistance to antimalarial drugs throughout the world. (Adapted from Drug-resistant malaria. Available at <http://www.cdc.gov/ncidod/emergplan/box23.htm>. Accessed 22 Oct 2002.)

ETIOLOGY AND CLINICAL MANIFESTATIONS

Malaria is caused by infection with 1 or more of the 4 *Plasmodium* species that infect humans: (1) *P. falciparum*, (2) *P. vivax*, (3) *P. ovale*, and (4) *P. malariae*. Of these infections, falciparum and vivax malaria account for the majority of infections. The likelihood of becoming infected with either of these species depends on the geographic region in which the person became infected. For example, most infections acquired in Africa are attributed to *P. falciparum*, whereas those acquired in Asia and the Americas are most often due to *P. vivax*.

Transmitted through the bite of an infected female *Anopheles* mosquito (Figure 3), the protozoan parasites cause hemolysis of infected erythrocytes and obstructed blood flow resulting from sequestration and sludging in the microcirculation. This disruption results in anoxia, lactic acidosis, and organ failure, most commonly in cases of falciparum malaria, in which severity and mortality correlate with the level of parasitemia. In nonimmune persons, parasitemia that is greater than 5% increases the risk for a fatal outcome.

The incubation period of the disease usually ranges from 9 to 30 days, after which time clinical symptoms

appear. With some strains of *P. vivax*, however, the incubation period can last as long as 9 to 12 months. Malaria chemoprophylaxis may also prolong onset of symptoms.

The well-known classic paroxysms of fever are absent at the beginning of the disease, when the presentation may be vague and nonspecific. Mild fever, chills, sweats, headache, and malaise are reported by most patients. Often mistaken for influenza or gastroenteritis, malarial symptoms also can include fatigue, nausea, myalgias, and occasional diarrhea. Uncomplicated malaria may be accompanied by systolic hypotension, jaundice, and hepatosplenomegaly. When severe, infection can result in organ failure (especially the brain, lungs, and kidneys), impaired consciousness, seizures, coma, and death.² A comparison of distinguishing clinical features associated with the different types of malaria is provided in Table 1.

LABORATORY DIAGNOSIS

Hemoglobin level and leukocyte count are often within normal limits in persons with uncomplicated malaria. However, thrombocytopenia and elevated levels of liver enzymes and serum lactate dehydrogenase

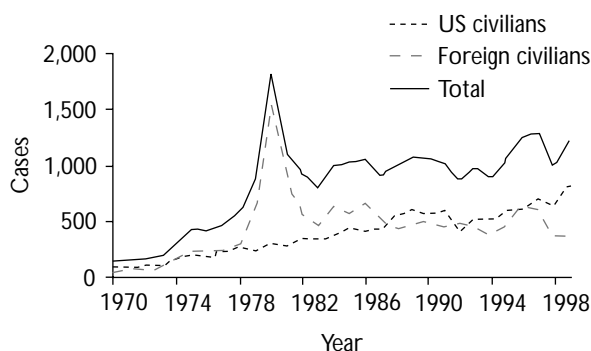


Figure 2. Number of malaria cases among US and foreign civilians in the United States, 1970 through 1999 (includes cases in Puerto Rico, Guam, and the US Virgin Islands). The substantial increase in the number of cases reported for 1980 primarily reflects cases diagnosed among immigrants from southeast Asia. (Adapted from Newman RD, Barber AM, Roberts J, et al. Malaria surveillance—United States, 1999. *MMWR Surveillance Summaries* 2002;51[SS-1]:15–28. Available at <http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5105a2.htm#fig1>. Accessed 22 Oct 2002.)



Figure 3. Female *Anopheles* mosquito, the vector of malaria. (Reprinted from the Centers for Disease Control and Prevention Public Health Information Library [photograph by Jim Gathany]. Available at <http://phil.cdc.gov/phil/detail.asp?id=1664>. Accessed 30 Oct 2002.)

are seen in more than half of infected persons. Three thick blood films should be examined, separated by an interval of 12 to 24 hours.² Alternatively, antigen detection using monoclonal antibodies and examination of acridine dye–stained buffy coat preparations can be used to diagnose falciparum malaria. In cases in which parasite morphology is either uncertain or potentially altered by drug therapy or improper sample handling, molecular diagnostic tests may be helpful. The CDC currently uses nested polymerase chain reaction assays for detection and speciation of *Plasmodium* species.⁶

RISK FACTORS DURING TRAVEL

The risk for acquiring malaria varies according to geographic area, altitude, season, time of day, specific setting (urban versus rural), duration of stay in an endemic area, type of accommodations, and compliance with preventive measures.⁷ For example, the risk for infection in the major cities of southeast Asia and South America is quite low, compared with the major cities of India, Pakistan, Bangladesh and sub-Saharan Africa. High elevations in Kenya, Ethiopia, Indonesia, and certain South American countries (eg, Peru, Ecuador, Colombia) pose little risk of transmission compared with lower altitudes. In some areas, malaria transmission is closely linked to seasonal rainfall and favorable environmental conditions for breeding of anopheline vectors. Therefore, the initial steps to

reduce malarial risk in persons traveling to malaria-endemic areas should include knowing their itinerary, estimating potential exposure to anopheline mosquitoes, and providing guidance with regard to taking appropriate precautions to avoid mosquito bites.

A number of personal protective measures have been shown to substantially decrease infection risk. Minimizing outdoor activities at dusk, wearing long-sleeved shirts and long pants sprayed with a permethrin repellent, and application of diethyltoluamide (DEET) (> 35%) to exposed skin are practical and effective measures. Because of the risk for central nervous system toxicity in young children, products containing lower concentrations of DEET should be applied sparingly and washed off when exposure risk decreases. Proper use of mosquito netting, especially permethrin-treated nets, has been shown to provide excellent protection during sleeping hours when mosquito feeding activities are at their highest.⁷ Burning pyrethroid mosquito coils in bedrooms at night can also be helpful.

In addition to assessing and minimizing exposure risk, physicians need to be aware of specific medical conditions that might affect disease severity or pose contraindications to the use of a particular antimalarial drug (eg, pregnancy); they should also determine patients' potential exposure to drug-resistant parasites. Moreover, prior to travel, patients should be provided with information regarding access to medical care if

Table 1. Distinguishing Clinical Characteristics of Malaria by Infectious *Plasmodium* Species

	<i>P. falciparum</i>	<i>P. vivax</i>	<i>P. ovale</i>	<i>P. malariae</i>
Average incubation period (days)	10–14	10–14	10–14	27–40
Severity of paroxysms	+	++	+	++
Duration of paroxysms (hours)	36 (maximum)	Fewer than 12	Fewer than 12	Fewer than 12
Duration of untreated primary attack (weeks)	2 to 3	3 to 8	2 to 3	3 to 4*
Microvascular disease	+	–	–	–
Anemia	++++	++	+	++
CNS involvement	++++	+	±	+
Renal involvement	+	±	+	++++
Complications	Seizures, coma, hypoglycemia, acidosis, pulmonary edema, disseminated intravascular coagulation, circulatory collapse	Splenic rupture (2–3 months after initial infection)		Immune complex glomerulonephritis/nephrotic syndrome

*Low-grade parasitemia may persist for many years.

needed during travel. The CDC and World Health Organization provide up-to-date information about country-specific malarial risk and recommendations for preventing and treating infection in travelers; these resources can be accessed via the Internet (at <http://www.cdc.gov/travel> and <http://www.who.int/ith>). Other CDC sources for recommendations regarding malaria prophylaxis and treatment are shown in **Table 2**. Finally, the *Medical Letter on Drugs and Therapeutics* publishes a biannual article on drugs appropriate for parasitic infections, which contains a section on prevention of malaria, including a list of countries in which risk for malaria exists and information about prophylaxis.⁸

CHEMOPROPHYLAXIS

General Principles

Before specific drugs used in malaria chemoprophylaxis are discussed, a review of the terminology used to describe how different classes of drugs work in malaria prevention is appropriate. Those drugs that kill asexual blood stages of plasmodia before they cause disease are called *suppressive chemoprophylactics*. Although suppressive chemoprophylaxis has no effect on liver stages of infection, trophozoites in erythrocytes are killed, as

long as adequate levels of drug in the blood are maintained. A loading dose is necessary to prevent primary detectable parasitemia, and postexposure prophylaxis is administered to prevent seeding of the bloodstream by parasites harbored in the liver. *Causal prophylaxis* involves drugs that prevent infection by eliminating liver stages of the parasite before they reach the bloodstream. These drugs are taken during the period of exposure and for several days afterward. They prevent primary detectable parasitemia as well as relapse. *Terminal prophylaxis* refers to the administration of therapy immediately after exposure to the relapsing vivax and ovale malarials in an attempt to prevent emergence of liver stages and subsequent parasitemia.

It is necessary to emphasize, however, that chemoprophylaxis does not guarantee protection against malaria. Consequently, for as long as a year after a person travels to an area where malaria is endemic, but especially within the first 2 months, malaria should be considered in the differential diagnosis of any febrile illness.

Prophylactic Agents

Table 3 outlines different chemosuppressive regimens, according to drug-resistance zones, and provides information about recommended dosages.

Table 2. CDC Sources for Recommendations Concerning Malaria Prophylaxis and Treatment

Type of Information	Source	Time Available	Telephone Number
Prophylaxis	CDC travelers' health hotline	24 hours per day, 7 days per week	877-FYI-TRIP (877-394-8747)
Prophylaxis	CDC travelers' health fax	24 hours per day, 7 days per week	888-232-3299
Prophylaxis	<i>Health Information for International Travel, 2001–2002</i>	Available by writing to the Superintendent of Documents, US Government Printing Office (GPO), Washington, DC 20402-9371 or by ordering from the Public Health Foundation Training Resource Center, at http://bookstore.phf.org/prod159.htm	202-512-1800
Treatment	CDC Malaria Epidemiology Branch	8:00 AM to 4:30 PM (EST), Monday through Friday 4:30 PM to 8:00 AM (EST), Monday through Friday (also 24 hours daily on weekends and on Federal holidays)	770-488-7788 404-639-2888 (Ask operator to page person on call for malaria section)

CDC = Centers for Disease Control and Prevention.

Adapted from Holtz TH, Kachur SP, MacArthur JR, et al. Malaria surveillance—United States, 1998. *Mor Mortal Wkly Rep CDC Surveill Summ* 2001;50(5):1–20.

Chloroquine phosphate. Once the mainstay of anti-malarial treatment, chloroquine use today is limited to preventing infection in only a few areas unaffected by widespread resistance to falciparum drugs. In Mexico, the Caribbean, Central America, Argentina, and parts of the Middle East and China, chloroquine is still considered the drug of choice for prevention of malaria. Chloroquine-resistant *P. vivax* has been reported in Papua, New Guinea, as well as in the Solomon Islands, Myanmar, and parts of Indonesia and India.⁹

One of the most desirable features of the drug is its safety in children and pregnant women. Although generally considered to be well tolerated, chloroquine has been associated with nausea, headache, dizziness, blurred vision, and pruritis, especially in dark-skinned persons. It may also worsen symptoms of psoriasis.

The recommended adult dosage of chloroquine is 500 mg salt once weekly with food. It should be started one week before departure to a malaria-endemic area and continued once a week, on the same day each week, during the period of malarial risk. To complete the course, the drug must be taken for an additional 4 weeks after returning to a risk-free area.¹⁰

Hydroxychloroquine sulfate. The adult dosage is 400 mg salt once a week, taken according to the same

schedule as for chloroquine phosphate. Adverse effects are similar to those of chloroquine sulfate, although they may be somewhat better tolerated.

Mefloquine. With demonstrated protective efficacy (> 90%) against drug-resistant malaria, mefloquine is a highly effective and convenient suppressive prophylactic agent. Significant resistance is known to occur only in the eastern and western border areas of Thailand.^{7,11} The adult dose is a single weekly tablet (250 mg salt) taken with food while in a malaria-endemic region and for 4 weeks after leaving the risk area. It is advisable to begin a loading regimen 2 weeks before potential exposure. Alternatively, when fewer than 2 weeks are available before departure to a malaria-endemic area, an accelerated loading schedule of 1 tablet daily for 3 days can be employed.⁷

Some physicians and patients have been reluctant to use mefloquine because of its reputation for causing nightmares, vivid dreams, mood disturbances, insomnia, dizziness, and headache. In actuality, adverse effects with mefloquine are generally mild and self-limited, appearing by the third dose in 75% of recipients.^{7,11} The drug is contraindicated in persons with a history of seizures, psychiatric disorders, or cardiac conduction abnormalities or arrhythmias.¹⁰ Although there have

Table 3. Malaria Chemosuppressive Regimens According to Zones of Drug Resistance

Zone	Drug of Choice	Alternatives
No chloroquine resistance	Chloroquine phosphate 300 mg base (500 mg salt) orally once weekly	Doxycycline 100 mg orally once daily
Chloroquine resistance	Mefloquine 228 mg base (250 mg salt) orally once weekly or Doxycycline 100 mg orally once daily or Atovaquone-proguanil 1 tablet (250 mg atovaquone/100 mg proguanil) daily	Primaquine 15 mg base (26.3 mg salt) orally once daily for 14 days after departure from malaria-endemic area or Chloroquine phosphate 300 mg base (500 mg salt) orally once weekly plus either pyrimethamine-sulfadoxine 3 tablets (75 mg pyrimethamine/1500 mg sulfadoxine) orally as a single dose for presumptive treatment or proguanil (Paludrine)*
Chloroquine and mefloquine resistance	Doxycycline 100 mg orally once daily or Atovaquone-proguanil 1 tablet (250 mg atovaquone/100 mg proguanil) daily	Primaquine 15 mg base (26.3 mg salt) orally once daily for 14 days after departure from malaria-endemic area or Chloroquine phosphate 300 mg base (500 mg salt) orally once weekly plus either pyrimethamine-sulfadoxine 3 tablets (75 mg pyrimethamine/1500 mg sulfadoxine) orally as a single dose for presumptive treatment or proguanil (Paludrine)

*Proguanil (Paludrine) is not available in the United States but is widely available in Canada and overseas. It is recommended mainly for use in Africa, south of the Sahara desert. Prophylaxis is recommended during exposure and for 4 weeks afterwards. Proguanil has been used in pregnancy without evidence of toxicity.

been no reports of birth defects attributed to mefloquine, it should be used cautiously in pregnancy, because it may result in an increased risk for stillbirth.¹²

Doxycycline. Doxycycline is a suppressive chemoprophylactic with activity against *P. falciparum* and *P. vivax*, including multidrug-resistant strains, comparable to that of mefloquine.¹³ The drug must be taken every day at the same time of day to be effective, starting 1 to 2 days before potential exposure and continuing for 4 weeks after leaving a high-risk area. When doxycycline fails to prevent infection, the main reason is noncompliance with the daily regimen.

Doxycycline should be taken with a meal to minimize gastrointestinal upset. The recumbent position should be avoided for at least an hour after ingestion to prevent reflux into the esophagus and esophageal ulceration. Photosensitivity is a concern, as are rashes and vaginal yeast infections. Doxycycline is contraindicated during pregnancy and should not be taken by lactating women or children younger than 8 years because of its adverse effects on tooth and bone development.¹⁰

Atovaquone-proguanil. This fixed-dose combination drug, formulated as 250 mg of atovaquone and 100 mg of proguanil hydrochloride, was approved by the Food and Drug Administration (FDA) in July 2000 as an alternative for malaria prophylaxis.¹⁴ Atovaquone, a hydroxynaphthaquinone analogue of ubiquinone, has a unique mechanism of action, selectively inhibiting parasite mitochondrial electron transport and membrane depolarization. Proguanil is believed to act synergistically with atovaquone through potentiation of its effect on parasite mitochondrial membrane potential.^{15,16}

Atovaquone-proguanil is active against the erythrocytic and exoerythrocytic forms of *P. falciparum*, including strains resistant to chloroquine, mefloquine, and pyrimethamine-sulfadoxine, and against the erythrocytic stages of *P. vivax*. Because the drug exhibits causal prophylactic activity against *P. falciparum*, it can be taken as a single daily tablet, starting 1 to 2 days before travel to a malaria-endemic area and continuing for a week after return.¹⁰ Several clinical trials of the drug have demonstrated protection comparable or superior to that of mefloquine, as well as an excellent safety profile.¹⁷⁻¹⁹

The most frequently reported adverse effects include nausea, vomiting, abdominal pain, diarrhea, and headache in approximately 10% to 15% of adults and children; mild transient asymptomatic elevations in serum transaminase and amylase levels have been reported in 5% to 10% of persons taking the drug.² Atovaquone-proguanil should not be taken by patients with severe renal dysfunction. Although proguanil is considered safe for use in pregnancy, atovaquone has been shown to be teratogenic in rabbits and has been classified as FDA category C.^{2,4,15}

Primaquine. Well-known for its effectiveness in treating cases of relapsing vivax or ovale malaria because of its ability to eliminate latent liver parasites (ie, terminal prophylaxis), this 8-aminoquinolone also demonstrates causal prophylactic activity; however, it is not licensed for this indication.²⁰ In clinical trials in which it was given in dosages of 30 mg base daily, primaquine demonstrated a protective efficacy of 85% to 95% against infection with *P. falciparum* and *P. vivax*.^{21–24} Daily primaquine, beginning 1 day before departure and continuing until 2 days after return from a malarious area, has been shown to provide effective prophylaxis against chloroquine-resistant *P. falciparum*.

Primaquine is generally well tolerated, causing only relatively mild nausea and abdominal distress, both of which can be further minimized by taking the drug with food. Its major drawback is its ability to cause methemoglobinemia (although generally mild) and hemolytic anemia in persons whose erythrocytes are deficient in glucose-6-phosphate dehydrogenase (G6PD). Patients should be screened for this deficiency before use of this drug is considered. It is contraindicated for use during pregnancy.⁸

Tafenoquine. This investigational synthetic analogue of primaquine appears to have greater potency and a better safety profile than primaquine, although hemolytic anemia in G6PD-deficient persons is still a concern. In ongoing trials in which the drug has been dosed on a weekly schedule of 200 mg base or 400 mg base because of its long plasma half-life (2–4 weeks), tafenoquine appears to offer a protective efficacy against *P. falciparum* of at least 90%. Of particular interest, a 3-day loading dose may provide protection for several weeks.²⁵ This feature may have important implications for its use in short-term travel to malaria-endemic areas.

Azithromycin. This macrolide antibiotic, commonly used to treat bacterial infections, has been examined in small field trials for its activity against *P. falciparum* and *P. vivax*. Despite encouraging results against *P. vivax*, its efficacy against *P. falciparum* has been shown to be only approximately 70%, which is signifi-

cantly less than the efficacy of either mefloquine or doxycycline.^{26,27} This fact, coupled with the need to take the drug on a daily basis, makes it much less desirable as a prophylactic agent. However, it may have a limited role in selected populations, such as pregnant women.

TREATMENT OF MALARIA

Because malaria chemotherapy is a complex therapeutic area, often requiring clinical expertise in tropical medicine and infectious diseases, a detailed description of treatment strategies is beyond the scope of this article. However, every clinician caring for patients who could potentially be infected with malaria should have a fundamental understanding of the disease, its diagnosis, and the importance of instituting prompt appropriate treatment. Therefore, a brief overview of currently available regimens, as well as options that may be available in the future, is provided. Physicians need to remind their at-risk patients that malaria is a serious, potentially fatal disease for which medical attention should be sought at the first sign of fever or flu-like symptoms.

Standby Malaria Therapy

Persons without access to reliable medical care within 24 hours may require standby therapy should symptoms suggestive of malaria develop, despite adherence to recommended prophylaxis. Pyrimethamine/sulfadoxine (Fansidar) has traditionally been used as the presumptive self-treatment of chloroquine-resistant malaria if the infected person is not allergic to sulfa drugs and for some reason has been unable to follow appropriate prophylaxis. The recommended dose is 3 tablets, taken as a single dose. It is important to ascertain that the travel itinerary does not include areas where resistance to the drug has been documented, such as the Amazon basin, southeast Asia, and certain countries in eastern and southern Africa. In areas with strains resistant to the drug, atovaquone-proguanil—4 tablets taken daily either as a single dose or as 2 doses (ie, 2 tablets per dose) for 3 consecutive days—may also be used for presumptive self-treatment in persons who are not taking the drug for prophylaxis. Alternatively, atovaquone (200 mg twice daily for 3 days) plus doxycycline (100 mg twice daily for 3 days) can also be used for presumptive treatment.^{8,10} Mefloquine is not recommended for self-treatment under these circumstances.

Recommended Treatment Regimens

Chloroquine remains the treatment of choice for nonfalciparum malaria.⁸ Exceptions include malaria

acquired in New Guinea, the Solomon Islands, Myanmar, and parts of Indonesia and India, where chloroquine-resistant *P. vivax* has been found.²⁹ *P. falciparum* malaria may be treated with chloroquine, provided that the infection was acquired in an area where drug resistance has not been described. For chloroquine-resistant strains, either mefloquine or quinine in combination with doxycycline or pyrimethamine/sulfadoxine is acceptable, although quinine is considered the drug of choice for severe malaria.^{9,28}

Multidrug-resistant strains can be treated with atovaquone-proguanil or mefloquine plus an artemisinin derivative (either artemether or artesunate), if available.²⁸ Artemisinin is the active component of the Chinese herb qinghao; its derivatives have been used in China and southeast Asia for the treatment of drug-resistant falciparum malaria, but they are not available in many western countries. Finally, although the drug halofantrine is effective against mild to moderate falciparum or vivax malaria, its usefulness is limited by its tendency to cause prolonged QT intervals and cardiac arrhythmias.

Emerging Therapies

Novel drug combinations (eg, atovaquone-proguanil) that offer the potential advantages of additive or synergistic antimalarial activity and less parasite resistance may be more effective than single agents in improving clinical outcomes. A number of promising new compounds are under development, including endoperoxides, quinolines, inhibitors of plasmodial phosph metabolism, and dihydrofolate reductase inhibitors.²⁹ The feasibility of reversing chloroquine resistance using histamine receptor blockers and calcium antagonists and of focusing on new therapeutic targets, such as plasmodial proteases, sodium/proton exchange, processes involved in erythrocyte invasion, and the plastid-like organelle required for parasite growth, are all being investigated. Despite many problems that confront our efforts to prevent malaria-associated morbidity and mortality, it is hoped that these new therapeutic avenues will lead to the development of more sophisticated and effective strategies to combat this global disease. **HP**

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(continued on page 68)

(from page 22)

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