Malaria: Epidemiology, Pathogenesis, Diagnosis, Prevention, and Treatment—An Update

EDWARD T. RYAN

EPIDEMIOLOGY

Overview
An estimated 300 million cases of malaria occur each year, annually accounting for 1.5 to 2.7 million deaths (1). Most of these deaths are due to infection with *Plasmodium falciparum* and occur among children and pregnant women in the developing world, especially sub-Saharan Africa. Unfortunately, mortality during severe or complicated malaria still exceeds 10% to 30% (2). Due to increasing resistance among malaria parasites to chemotherapeutic agents, dissolution of malaria control programs, and increasing international travel, the incidence of malaria is increasing worldwide. Large scale multinational efforts have been initiated to “roll back malaria,” including major commitments of financial, clinical, and research resources (3,4).

Malaria in Travelers
Although the overwhelming majority of morbidity and mortality associated with malaria occurs in the developing world, this disease also affects travelers. Without chemoprophylaxis, a traveler’s risk of acquiring malaria is highest in areas of Oceania (more than 20% per month in regions of New Guinea) and in sub-Saharan Africa (approximately 2% per month); the risk is intermediate in South Asia (0.1% to 0.01% per month); and lowest in the Americas and Southeast Asia (less than 0.01% per month) (5–7). Each year, approximately 30,000 individuals who travel from industrialized nations to the developing world contract malaria, and more than 1000 cases of malaria are reported to the Centers for Disease Control and Prevention (CDC) in the United States (8,9).

Malaria in travelers is largely preventable: most occurrences are due to inadequate or incorrect pre-travel advice or lack of compliance with a recommended chemopro-
phylactic regimen (11). Drug resistance is also increasingly being recognized as a contributing factor (11). In the United States, mortality from malaria is approximately 4%, with mortality increasing to 30% in individuals older than 70 years of age (10,12).

### Drug-Resistant Malaria

Table 4.2 lists selected antimalarial drugs, outlining both those agents’ mechanisms of action and the mechanisms by which organisms develop resistance to those drugs (13–30,123).

Chloroquine-resistant *P. falciparum* has been reported in all malarious areas except Central America west of the Panama Canal, the island of Hispanola (Haiti and the Dominican Republic), and certain areas of the Middle East (31,32). Mefloquine-resistant *P. falciparum* infection has been observed in the western provinces of Cambodia, the eastern provinces of Myanmar (Burma), and the Thailand–Myanmar and Thailand–Cambodia border areas (32). Widespread resistance of *P. falciparum* to sulfadoxine-pyrimethamine has been documented in many areas of the world, including sub-Saharan Africa, South Asia, South Asia, Oceania, and the Amazon basin (22,31). Chloroquine-resistant *P. vivax* is reported in areas of Oceania, including Indonesia, Papua-New Guinea, Vanuatu and the Solomon Islands, as well as India, Thailand, Myanmar, and South America, including Brazil, Guyana, and Peru (31,33–36). Strains of *P. vivax* that are tolerant, or even resistant, to primaquine are found in areas of Southeast Asia and East Africa, including Somalia (37–40).

### PATHOGENESIS

#### Antigenic Variation

Erythrocytes infected with *P. falciparum* form electron-dense, knoblike structures on their surface membranes. These structures become involved in the adhesion of infected ery-
throphocytes to vascular endothelium, and they may be possibly involved in erythrocyte rosetting (41). The knobs are composed of both host and parasite proteins, including the parasite proteins KAHRP (knob-associated histidine-rich protein) and PfEMP-1 (*P. falciparum* erythrocyte membrane protein-1) (41). The large (250 to 320 kDa) PfEMP-1 proteins are encoded by the *var* (“variety”) family of genes (42–46). Approximately 150 *var* genes have been identified to date, although the number that are functional is not currently known (45,47). A number of *var* genes may be transcribed within a specific *P. falciparum* parasite,
but only one \textit{var} gene is dominantly expressed on the surface of an infected erythrocyte at any given time (48,49).

\textit{PfEMP-1} proteins are involved in cytoadhesion of \textit{P. falciparum}-infected erythrocytes to thrombospondin (TSP) and several endothelial cell receptors, including CD36, intercellular adhesion molecule 1 (ICAM-1), vascular adhesion molecule (VCAM), and endothelial leukocyte adhesion molecule (ELAM) (Figure 4.1) (45,50–54). Infected erythrocytes expressing a \textit{PfEMP-1} protein that binds ICAM-1 have been associated with cerebral malaria (55,56). In addition, \textit{PfEMP-1} proteins have been identified that mediate binding of infected erythrocytes to chondroitin sulfate A and hyaluronic acid—both molecules that are expressed in large amounts in placental tissue; this relationship may partly explain the placental sequestration of infected erythrocytes during pregnancy (52). After targeted cytoadhesion, local tissue hypoxia and nitric oxide production ensue, contributing to the malarial pathophysiology (57). Specific binding of \textit{P. falciparum}-infected erythrocytes to endothelial cells of placental tissue is also mediated by non-\textit{PfEMP-1} proteins (58).

In addition to \textit{var} genes, a number of other multigene families have been identified in \textit{P. falciparum}, including \textit{stevor}, \textit{rif}, and \textit{Pf60} gene families (59,60). Proteins encoded by \textit{stevor} and \textit{rif} are variable surface antigens of unknown function (although \textit{rif} products are involved in rosette formation of infected erythrocytes) (4,60). Proteins encoded by \textit{Pf60} remain in the nucleus and have an unknown function (59).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.1.png}
\caption{Schematic of a \textit{P. falciparum}-infected erythrocyte expressing a \textit{PfEMP-1} with anti-CD36 binding capacity. Other endothelial surface molecules represented are intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule (VCAM), and endothelial leukocyte adhesion molecule (ELAM).}
\end{figure}
Immunity

Immunity to malaria develops over several years of almost continuous exposure and infection. It is characterized by a gradual decrease in the frequency and severity of clinical disease. Repetitive waves of antigenic variation may account for this gradual onset of immunity (61–64). Recent work has also elucidated more about the nature of immunity:

- Erythrocytes infected with \textit{P. falciparum} also adhere to dendritic cells, inhibiting their maturation and reducing their capacity to stimulate T cells (65).
- Cohabitating strains of malaria (strains of the same species of plasmodium simultaneously present within a host) influence each other's survival by downregulating cellular immune responses through altered peptide ligand antagonism of naturally occurring variant cytotoxic T-cell epitopes (66,67).
- Cross-species interactions of malaria parasites result in nonindependent, sequential episodes of infection with different species of plasmodia (68).

Immunization with a malaria vaccine containing certain T-cell epitopes could, therefore, impede the ability to control infection with a strain expressing a related but distinct T-cell epitope (68). In addition, a malaria vaccine that proves successful against one species of malaria might possibly increase the incidence of disease due to another strain (68).

DIAGNOSIS

Worldwide, microscopy remains the tool of choice for diagnosing malaria. In comparison to analysis of blood by polymerase chain reaction (PCR), microscopy is 85% to 95% sensitive and 95% to 100% specific (69,70). Microscopic examination of peripheral blood stained with Giemsa, Wright's and Field's stains permits detection of 10 to 100 parasites per microliter of blood, and microscopy permits species identification. Microscopy is, however, time-consuming and requires sufficient operator expertise.

Fluorescent microscopy has also been used to identify malaria parasites (69). One such assay is the QBC Malaria Test system (Becton Dickinson, Sparks, Maryland). In this assay, a sample of blood is mixed in a capillary tube with acridine orange, microcentrifuged, and analyzed under fluorescent microscopy. Although it gives results more quickly than traditional microscopy (preparing, spinning, and reading the sample requires 10 minutes), species identification can be more problematic with this assay (71–73). Moreover, in comparison to thin- and thick-smear analysis, the QBC system is 70% to 100% sensitive and 85% to 95% specific, with its sensitivity falling to 40% to 70% when fewer than 100 parasites are present per microliter of blood (69,71,72,74–78). Although the QBC system is useful, the requirement for a fluorescent microscope and tabletop centrifuge has limited its use in much of the developing world.

More recently, a number of rapid diagnostic tests have been developed that detect parasite proteins in peripheral blood. Some of these tests detect malaria histidine rich protein II (HRPII), such as the ParaSight F-test (Becton Dickinson), the ICT Malaria P.f. test/MalaQuick (ICT Diagnostic, Sydney, Australia), the PATH \textit{P. falciparum} malaria IC strip (Program for Appropriate Technology in Health, Seattle, Washington), and the Determine Malaria Pf test (Abbot Laboratories, Japan) (79–81). Early versions of these assays detected only HRPII of \textit{P. falciparum}; newer-generation assays, however, detect antigens of both \textit{P. falciparum} and \textit{P. vivax} (such as the ICT Malaria P.f./P.v. test) (82). In addition, assays that detect all four malaria species are under development (69).
Another group of assays have been developed that detect plasmodial lactate dehydrogenase (pLDH) via immunochromatographic detection (OptiMAL kit; Flow, Inc., Portland, Oregon), or via enzymatic reaction (ICpLDH; Flow, Inc.) (83). The pLDH assays are able to detect antigens of both \textit{P. falciparum} and \textit{P. vivax} (84).

The diagnostic abilities of the various HRP and pLDH rapid assays are comparable. In comparison to thin- and thick-blood-smear analysis, these assays are approximately 90% to 95% sensitive and 85% to 95% specific, although sensitivity of the rapid assays is much lower (30% to 60%) in the presence of low parasitemia (fewer than 50 to 100 parasites per microliter of blood) and even occasionally in the presence of very high parasitemia (69,83,85–88).

Although the rapid diagnostic assays offer a number of attributes that make them attractive for use in the developing world (minimally trained personnel find them easy to use, no equipment is required, and samples can be read with the naked eye), they also have a number of disadvantages that limit their utility:

- The assays are unable to quantify the level of parasitemia (except for the ICpLDH assay) (83).
- They are currently unable to detect all malarial species.
- They are unreliable in the presence of low-level (and occasionally even very-high-level) parasitemia (88).
- They remain positive for 7 to 14 days after treatment (complicating discernment of relapsing, recrudescent, or cured malaria at follow-up visits) (86,89).
- They may give false-positive reactions in individuals with positive rheumatoid factor (especially HRP-detecting assays) (69,90,91).

Recent studies have also shown that these rapid diagnostic assays are dangerous when used by travelers to self-diagnose malaria (80). In this setting, false-negative interpretations are frequent in the presence of low-level parasitemia (and even with high-level parasitemia with some of the assays) (80). The assays are, however, useful when performed by trained laboratory personnel and probably will have their greatest utility in areas of the world with extremely limited resources or with limited expertise in microscopic diagnosis of malaria (92,93). The assays are also more sensitive than microscopic analysis of peripheral blood in identifying women with placental malaria (94).

PREVENTION OF MALARIA

Malaria can be prevented through interventions that minimize the number of mosquito bites, including the appropriate use of \(N, N\)-diethylmethyltoluamide (DEET)-containing insect repellents and permethrin-impregnated bednets and clothing (1,95–99). The disease can also be prevented through the judicious use of effective chemotherapeutic agents (Table 4.3). Unfortunately, the use of chemotherapeutic agents remains impractical in much of the developing world, although targeted use during pregnancy can be beneficial (100–102). In such areas, both chloroquine prophylaxis and intermittent presumptive treatment with sulfadoxine-pyrimethamine during pregnancy are safe and may be effective (100–102). Although prophylactic use of mefloquine in pregnant women is also safe and more effective than chloroquine in preventing malaria, mefloquine's expense has limited its use (103–105).

The decision to use a chemoprophylactic agent to prevent malaria in a traveler should
weigh that individual’s risk of acquiring malaria against the possibility that the person will develop an adverse reaction to the selected agent. The selection of an agent (or the choice to use no agent at all) should reflect the traveler’s medical condition and medications taken, the time of year of travel, the individual’s destination, the susceptibility of malaria parasites to various agents in that destination, and the person’s overall risk of acquiring malaria. Resources giving standard recommendations on the prevention of malaria should be consulted when advising travelers (32,106,107). Note that travelers to certain destinations, including most urban areas and tourist destinations in Latin America and Southeast Asia, often require no chemoprophylaxis, although they should practice behavioral modification to limit their risk of insect-borne diseases, including the use of insect repellents.

**Chloroquine**

Chloroquine is the drug of choice for prophylaxis of individuals at high risk of acquiring malaria who are traveling to areas of the world in which chloroquine-resistant malaria has not been reported (32,107). The most common side effect associated with this agent is pruritus, which is usually most severe in individuals of African descent. Chloroquine can exacerbate psoriasis or porphyria. When extremely high dosages of chloroquine are ingested over prolonged periods, retinopathy may develop (108). In addition, this drug can cause cardiac arrhythmias, especially in individuals with underlying arrhythmic disorders of the heart, including prolonged QT syndrome (108).

Chloroquine’s bitter taste usually requires that it be mixed with a sweet agent for consumption by young children (109). Nursing children should be given an individual dose of chloroquine because insufficient quantities are expressed in breast milk.

Concomitant use of chloroquine and intradermal administration of human diploid cell rabies vaccine (HDCV) can result in lower immune responses to the vaccine (32,109). Intradermal administration of HDCV should be completed seven days before beginning chloroquine prophylaxis; alternatively, HDCV can be given intramuscularly or another rabies vaccine can be administered without concern for interaction.

Amodiaquine is an aminoquinoline related to chloroquine that is used in some areas of the world. Its association with rare, but idiosyncratic toxic hepatitis and agranulocytosis has limited its use (110).

**Mefloquine**

Mefloquine is a 4-quinoline methanol with a half-life of 7 to 30 days. In the United States, this drug is a chemoprophylactic agent of choice for individuals at high risk of acquiring chloroquine-resistant malaria (32). When used as a prophylactic agent, mefloquine is extremely effective, with efficacy rates exceeding 90% to 95% (5,7,111). It is usually extremely well tolerated by most individuals. Severe neuropsychiatric reactions, including seizures and psychosis, occur in approximately 1 in 10,000 to 1 in 13,000 users of prophylactic mefloquine, however. Fewer than 5% of individuals who use prophylactic mefloquine report milder neuropsychological adverse events, including sleep disturbances, insomnia, nightmares, cognitive changes, anxiety, or depression that are disabling enough to result in drug discontinuation(1,112–116). Long-term use of mefloquine has not been associated with additional adverse effects (111).

Mefloquine should not be used in individuals with underlying cardiac arrhythmias or conduction disturbances, individuals with a history of psychiatric illnesses such as psychosis
<table>
<thead>
<tr>
<th>Medication</th>
<th>Adult Dose</th>
<th>Pediatric Dose</th>
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<tbody>
<tr>
<td>Chloroquine-sensitive areas‡</td>
<td>Chloroquine phosphate 300 mg base (500 mg salt) once per week, beginning 1 to 2 weeks before entering and continuing until 4 weeks after leaving malarious area</td>
<td>5 mg/kg base (8.3 mg/kg salt), up to adult dose, once per week, as for adults</td>
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<tr>
<td>Chloroquine-resistant areas§</td>
<td>Mefloquine§ 228 mg base (250 mg salt) in United States (250 mg base outside United States) once per week, beginning 1 to 2 weeks before entering and continuing until 4 weeks after leaving malarious area§</td>
<td>&lt;15 kg: 5 mg/kg (salt); 15–19 kg: 1/4 tablet; 20–30 kg: 1/2 tablet; 31–45 kg: 3/4 tablet; &gt;45 kg: 1 tablet, once per week, as for adults§</td>
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<tr>
<td>OR</td>
<td>Doxycycline¶ 100 mg once per day, beginning 1 to 2 days before entering and continuing until 4 weeks after leaving malarious area</td>
<td>2 mg/kg/day, up to adult dose, as for adults¶</td>
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<tr>
<td>OR</td>
<td>Atovaquone/proguanil</td>
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## Alternatives

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<tr>
<th><strong>Primaquine</strong>&lt;sup&gt;**&lt;/sup&gt;</th>
<th>30 mg base once per day, beginning 1 to 2 days before entering and continuing until 7 days after leaving malarious area</th>
<th>0.5 mg/kg base daily, up to adult dose, as for adults</th>
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<tr>
<td><strong>OR</strong></td>
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<tr>
<td><strong>Chloroquine phosphate</strong></td>
<td>See above</td>
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<tr>
<td><strong>PLUS proguanil</strong>††</td>
<td>200 mg once per day, beginning 1 to 2 days before entering and continuing until 4 weeks after leaving malarious area</td>
<td>&lt;2 years: 50 mg; 2–6 years: 100 mg; 7–10 years: 150 mg; &gt;10 years: 200 mg, daily, as for adults</td>
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### Mefloquine-resistant areas<sup>‡</sup>

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<tr>
<th><strong>Doxycycline</strong>&lt;sup&gt;¶&lt;/sup&gt;</th>
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<tbody>
<tr>
<td><strong>Atovaquone/proguanil</strong>‡‡</td>
<td>See above</td>
<td>See above</td>
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<sup>**If an individual is at high risk of contracting malaria and is taking chemoprophylaxis, consider primaquine phosphate 15 mg base (children 0.3 mg/kg base, up to adult dose) daily for last two weeks of chemoprophylaxis to decrease likelihood of late-onset malaria due to *P. vivax* and *P. ovale*. Do not give if the patient is glucose 6-phosphate dehydrogenase deficient or pregnant. Not required if the chemoprophylaxis used during exposure is primaquine.**

<sup>† Presumptive self-treatment of malaria is not routinely recommended; individuals with fever at risk for malaria should seek medical attention. Expert advice may be beneficial for travelers who will be unable to obtain timely medical care and for travelers who cannot take the optimal prophylaxis.</sup>

<sup>‡ Chloroquine-resistant *P. falciparum* has been reported in all malarious areas except Mexico, Central America west of the Panama Canal, Haiti, the Dominican Republic, and scattered areas of the Middle East. Mefloquine-resistant *P. falciparum* has been reported in Western provinces of Cambodia, Eastern provinces of Myanmar (Burma), and the border regions between Thailand and Myanmar and between Thailand and Cambodia.</sup>

<sup>§ Mefloquine may be administered weekly for three weeks before entering a malarious area, or it may be front-loaded with daily dosing for three consecutive days (of normal weekly dose), then weekly until four weeks after leaving the malarious area. Mefloquine should not be used by individuals with a history of psychiatric illness, seizures, or cardiac conduction abnormalities. It is not approved for use during pregnancy, although its use at prophylactic dosages is probably safe, especially during the second and third trimesters. Limited data suggest that it is safe during the first trimester. The pediatric dosage is not approved by the U.S. Food and Drug Administration (FDA), but is recommended by the Centers for Disease Control and Prevention.</sup>

<sup>¶ Do not use in pregnant women and children younger than 8 years of age. Doxycycline can cause photosensitivity and vaginal moniliasis, and it can decrease the efficacy of hormonal contraceptive agents. Take with food; do not simultaneously use antacids or bismuth-containing products and doxycycline.</sup>

<sup>‡‡ Preliminary data suggest atovaquone/proguanil is effective in the prevention of malaria caused by multi-drug resistant *P. falciparum*. Efficacy against other species of malaria may be lower.</sup>

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and anxiety disorders, and individuals with a history of seizures. The drug is commonly used in children who are at high risk of acquiring chloroquine-resistant malaria (32). Although specific pediatric dosages have not been approved by the U.S. Food and Drug Administration, they are recommended by the CDC (32).

Because it takes six to nine weeks to achieve therapeutic blood levels of mefloquine with standard weekly dosing (117), some authorities recommend that individuals begin mefloquine prophylaxis two to three weeks before they enter a malarious area. Alternatively, mefloquine may be taken as a once-daily dose (of the weekly dose) consecutively for three days, one to two weeks before entering a malarious area (109,117,118). Such “front-loading” achieves therapeutic blood levels in approximately four days (109,117,118) and permits early identification of individuals who are intolerant of mefloquine (109,119). Approximately 2% of “front-loaded” individuals will discontinue mefloquine prophylaxis, usually because of dizziness or gastrointestinal upset (109,119).

**Doxycycline**

Doxycycline may be used by individuals at risk of chloroquine-resistant malaria who cannot take mefloquine; it is also a drug of choice for all individuals at risk of malaria traveling to areas of the world reporting mefloquine-resistant malaria (7,32,109,120). When used as a prophylactic agent, doxycycline has a protective efficacy equivalent to that of mefloquine—that is, greater than 90% (1,7). The apparent lower efficacy of doxycycline relative to mefloquine is attributable to poor compliance with daily dosing (121).

Doxycycline should not be administered to children younger than 8 years of age, nor should it be used by pregnant or lactating women. Its adverse effects include the following:

- Photosensitivity—including sensitivity to both ultraviolet A and ultraviolet B light.
- Vaginal moniliasis—especially in women who have a history of recurrent yeast infections.
- Decreased efficacy of hormonal contraceptive agents—women using such agents should use a backup mechanism of contraception for at least two cycles after stopping doxycycline.
- Gastrointestinal upset—doxycycline should be taken with a meal.
- Esophageal erosions—especially in individuals with gastroesophageal reflux or if the medicine is taken immediately before reclining; doxycycline should, therefore, be taken with an 8-oz glass of water and should not be taken at bedtime.
- Decreased absorption when ingested with heavy metals such as bismuth and those in antacids—doxycycline should not be taken simultaneously with these agents (109).

**Atovaquone and Proguanil**

Atovaquone is a hydroxynaphthoquinone that inhibits mitochondrial electron transport (122,123). Resistance to atovaquone develops rapidly when this agent is used alone (123,124). Proguanil hydrochloride is a prodrug that is metabolized in vivo to cycloguanil. This agent is both a blood and tissue schizonticide, inhibiting the growth of both blood and the pre-erythrocytic liver stage of the parasite. It is not effective against the latent hypnozoite intrahepatic forms of *P. vivax* and *P. ovale*, however (125). Resistance to proguanil develops rapidly when the agent is used alone.

The combination of atovaquone and proguanil acts synergistically against plasmodia
in vitro and in vivo (124,126). Interestingly, when proguanil is used with atovaquone, it appears to act as the parent molecule (proguanil), rather than as the metabolite (cycloguanil); that is, proguanil does not act as a dihydrofolate reductase inhibitor when used with atovaquone (24). The synergy with atovaquone appears to result from a lowering of the effective concentration at which atovaquone collapses mitochondrial membrane potential in malaria parasites (126).

Because of its unique mechanism of action, atovaquone has similar activity against both chloroquine-sensitive and chloroquine-resistant strains of \textit{P. falciparum}. Both atovaquone and proguanil have causal prophylactic activity against the liver stages of \textit{P. falciparum} (127). The combination therapy is not effective against the latent hypnozoite forms of \textit{P. vivax} and \textit{P. ovale}, however (128).

Three placebo-based clinical trials have examined prophylactic use of the atovaquone-proguanil combination in African adults and children with uncomplicated \textit{P. falciparum} malaria. In those studies, compared to placebo, daily atovaquone-proguanil was found to be safe, well tolerated, and 95% to 100% effective against \textit{P. falciparum} parasitemia (129–131). A number of completed or ongoing studies have evaluated (or are addressing) the prophylactic use of atovaquone-proguanil in nonimmune adults (132,133). In these studies, atovaquone-proguanil has been shown to be well tolerated and highly efficacious in preventing malaria caused by \textit{P. falciparum} (95%). The efficacy of atovaquone and proguanil as a prophylactic combination regimen against \textit{P. vivax}, \textit{P. ovale}, and \textit{P. malariae} has been less well studied, although preliminary data would suggest that the drug combination is less effective against \textit{P. vivax} (70–90%) than against \textit{P. falciparum} (95%) (124,134,135).

An atovaquone-proguanil combination (Malarone; GlaxoWellcome Inc., Research Triangle Park, NC) has recently become available in the United States for use as a prophylactic regimen against \textit{P. falciparum} malaria, including the prevention of chloroquine resistant \textit{P. falciparum}. The combination is well tolerated; infrequently reported adverse events include mild nausea, vomiting, abdominal pain and diarrhea, and transient asymptomatic elevations in serum hepatic transaminase and amylase values (1).

**Primaquine**

Primaquine is an 8-aminoquinoline antimalarial agent with causal prophylactic activity. It destroys pre-erythrocytic hepatic stages of the parasite.

Primaquine has historically been used as a terminal prophylactic agent to eradicate hepatic hypnozoite stages of \textit{P. vivax} and \textit{P. ovale} (the latent hepatic forms can result in relapses months or even years after primary infection). When used as a terminal prophylactic agent, this drug should be taken daily for two weeks after the person leaves a malarious area.

Daily primaquine (at 0.5mg/kg of base per day [up to 30mg]) may also be used as a primary causal prophylactic agent (136–139). When taken as a causal prophylactic, the drug should be taken one to two days before the person enters a malarious area and continued daily until two to seven days after the individual leaves the malarious area.

Primaquine may cause methemoglobinemia and oxidant-induced hemolytic anemia, especially in individuals with glucose-6 phosphate dehydrogenase deficiency (118). This agent should not be used in pregnant women. Even after one year of daily use, primaquine is well tolerated; the most frequently reported side effect is gastrointestinal upset, which can be ameliorated by taking the medication with food (108,118,136).
Tafenoquine

Tafenoquine (WR238605) is an 8-aminoquinoline agent related to primaquine (108,140,141). It has potent activity against both liver and blood asexual stages and sexual (gametocyte) stages of the malaria parasite. Tafenoquine appears to be better tolerated than primaquine (140). Whereas primaquine requires daily dosing, tafenoquine may be effective when taken as a single loading dose before a short trip or when taken weekly during travel. Its role in the prevention and therapy of malaria is currently being evaluated. As is the case with primaquine, its use is contraindicated in individuals with glucose 6-phosphate dehydrogenase deficiency and in pregnant women.

Chloroquine and Proguanil

The combination of daily proguanil with weekly chloroquine is more effective at preventing malaria in sub-Saharan Africa than is weekly chloroquine alone. Unfortunately, the protective efficacy of the chloroquine–proguanil combination is poor: it is 50% to 70% effective as compared with doxycycline or mefloquine (1,5,111,118,142). The combination of daily and weekly medications can also result in increased confusion and decreased compliance.

Proguanil is usually well tolerated, although oral ulcerations, pancytopenia, thrombocytopenia, and granulocytopenia have been associated with its use. This drug is not available as a single agent in the United States.

Azithromycin

Azithromycin is a macrolide antibiotic related to erythromycin. It shows some activity against plasmodia species, but its protective efficacy against P. falciparum infection is low (approximately 70% to 83%, even among partially immune adults). In addition, daily administration is required, and the agent is not causally prophylactic (1,143). No field trial has as yet examined the efficacy of azithromycin in preventing malaria in nonimmune adults. Although it is well tolerated, azithromycin is much more expensive than other, more effective agents. It should not be used as an agent to prevent malaria (135).

Prevention of Malaria in Pregnant Women and Children

Pregnant women and children are at increased risk of suffering severe adverse events from malaria. As a consequence, steps should be taken to prevent malaria in these individuals, including the appropriate use of DEET-containing insect repellents and permethrin-impregnated bednets and clothing (1,95–99).

Chloroquine can be safely administered to all pregnant women (that is, during all trimesters of pregnancy) and children. Doxycycline, primaquine, and tafenoquine should never be used during pregnancy, and doxycycline should not be used in children younger than 8 years of age. Proguanil has been employed safely during pregnancy and in small children. Note, however, that the combination of chloroquine and proguanil is not as effective as mefloquine. Atovaquone’s (and therefore atovaquone-proguanil’s) safety in pregnancy has not been established. Atovaquone-proguanil is, however, approved for use in children weighing more than 10kg, and a pediatric tablet is available.

The CDC has recommended the use of mefloquine in children of all ages and all weights who are deemed at high risk of acquiring chloroquine-resistant P. falciparum infec-
tion (32). (Atovaquone-proguanil may also be used in children weighing more than 10 kg.) No human study has linked prophylactic use of mefloquine during pregnancy with teratogenicity or congenital malformations in newborns (105,144–147). When mefloquine is administered as a prophylactic agent during the second and third trimesters of pregnancy, its use has not been associated with any significant adverse events in either the mother or the fetus (106,110,147). Some studies, however, have found an increased rate of miscarriage when mefloquine is used during the first trimester (145). Other studies have found no increased risk compared to background rates and compared to rates in women taking chloroquine, chloroquine-proguanil, or sulfadoxine-pyrimethamine (110,144,148).

Prophylactic use of mefloquine during pregnancy is, therefore, probably safe, especially during the second and third trimesters. Limited data also suggest that it is safe when used for prophylaxis during the first trimester (32).

At present, no safe and effective chemophylactic agent is available for children younger than 8 years of age and pregnant women traveling to mefloquine-resistant areas of the world (109). The combination of atovaquone and proguanil may be used in such individuals, but the safety of this combination in young children and pregnant women remains to be established.

TREATMENT

Table 4.4 lists the currently available options for treatment of malaria. In many areas of the world, individuals with malaria are treated as outpatients, often with an antipyretic agent and an inexpensive antimalarial agent such as chloroquine or sulfadoxine-pyrimethamine. Hospitalization and parenteral administration of antimalarial agents are usually reserved for individuals with severe or complicated malaria—that is, malaria associated with impaired consciousness, coma, seizures, renal failure, pulmonary edema, shock, severe acidosis, severe jaundice, hypoglycemia, and/or parasitemia levels greater than 5% to 15% (2,149,150) In industrialized countries, individuals with malaria, especially those with *P. falciparum* malaria, are usually treated as inpatients.

In North America, the most common errors in the management of individuals with malaria relate to the following:

- Failure to consider the diagnosis.
- Inappropriate choice of drug or route of administration.
- Misjudgment of the severity of infection.
- Failure to recognize and treat the complications of severe malaria (including severe hypoglycemia).
- Inappropriate management of fluid and electrolyte status.
- Failure to monitor clearance of parasitemia (11).

**Treatment of Chloroquine-Sensitive Malaria**

**Chloroquine** Oral chloroquine phosphate is the therapeutic agent of choice for individuals with uncomplicated infection with *P. ovale*, *P. malariae*, chloroquine-sensitive *P. vivax*, or chloroquine-sensitive *P. falciparum*. If chloroquine is not available, hydroxychloroquine sulfate may be used. Blood smears and clinical parameters should be followed, and
### Table 4.4  Treatment of malaria

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adult Dose</th>
<th>Pediatric Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORAL THERAPY</strong>†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloroquine-sensitive plasmodia‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloroquine phosphate§</td>
<td>600 mg base (1 g salt), then 300 mg base (500 mg salt) 6h later, then 300 mg base (500 mg salt) at 24 and 48h</td>
<td>10 mg base/kg (up to adult dose), then 5 mg base/kg 6h later, then 5 mg base/kg at 24 and 48h</td>
</tr>
<tr>
<td>Chloroquine-resistant <em>P. falciparum</em>‡¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atovaquone-proguanil (Malarone)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 tablets (250 mg-atovaquone/100 mg-proguanil) daily × 3 day</td>
<td>11–20 kg = 250 mg/100 mg 21–30 kg = 500 mg/200 mg 31–40 kg = 750 mg/300 mg &gt;40 kg = 1 g/400 mg, daily × 3 day</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinine sulfate</td>
<td>650 mg q8h × 3–7 day**</td>
<td>25 mg/kg/day (up to daily adult dose) in 3 doses × 3–7 day**</td>
</tr>
<tr>
<td><strong>PLUS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxycycline††</td>
<td>100 mg bid × 7 day</td>
<td>2 mg/kg/day (up to daily adult dose) × 7 day</td>
</tr>
<tr>
<td>OR PLUS tetracycline††</td>
<td>250 mg qid × 7 day</td>
<td>6.25 mg/kg (up to adult dose) qid × 7 day</td>
</tr>
<tr>
<td>OR PLUS Sulfadoxine-pyrimethamine‡‡ (Fansidar)</td>
<td>3 tablets at once on last day of quinine</td>
<td>&lt;1 yr: (\frac{1}{4}) tablet 1–3 yr: (\frac{1}{2}) tablet 4–8 yr: 1 tablet 9–14 yr: 2 tablets ≥15 yr: 3 tablets, as for adults</td>
</tr>
<tr>
<td>OR PLUS clindamycin§§</td>
<td>900 mg tid × 5 day</td>
<td>20–40 mg/kg/day (up to daily adult dose) in 3 doses × 5 day</td>
</tr>
</tbody>
</table>
## Alternatives

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mefloquine</strong>&lt;sup&gt;¶¶&lt;/sup&gt;</td>
<td>750mg once followed by 500mg 12h later</td>
</tr>
<tr>
<td><strong>Halofantrine</strong>&lt;sup&gt;***&lt;/sup&gt;</td>
<td>500mg q6h x 3 doses; repeat in 1 week&lt;sup&gt;†††&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Atovaquone</strong>&lt;sup&gt;‡‡‡&lt;/sup&gt;</td>
<td>500mg bid x 3 day</td>
</tr>
<tr>
<td><strong>PLUS</strong> proguanil**&lt;sup&gt;‡‡‡&lt;/sup&gt;</td>
<td>200mg bid x 3 day</td>
</tr>
<tr>
<td><strong>OR PLUS</strong> doxycycline&lt;sup&gt;††&lt;/sup&gt;</td>
<td>100mg bid x 3 day</td>
</tr>
<tr>
<td><strong>Artesunate</strong>&lt;sup&gt;***&lt;/sup&gt;</td>
<td>4mg/kg/d x 3 day</td>
</tr>
<tr>
<td><strong>PLUS</strong> mefloquine&lt;sup&gt;¶¶&lt;/sup&gt;</td>
<td>750mg once followed by 500mg 12h later</td>
</tr>
<tr>
<td><strong>Chloroquine-resistant <em>P. vivax</em></strong>&lt;sup&gt;‡§§§&lt;/sup&gt;</td>
<td>650mg q8h x 3–7 day&lt;sup&gt;***&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>PLUS</strong> doxycycline&lt;sup&gt;††&lt;/sup&gt;</td>
<td>100mg bid x 7 day</td>
</tr>
<tr>
<td><strong>OR PLUS</strong> Sulfadoxine-pyrimethamine&lt;sup&gt;‡‡&lt;/sup&gt; (Fansidar)</td>
<td>3 tablets at once on last day of quinine</td>
</tr>
<tr>
<td>Mefloquine&lt;sup&gt;¶¶&lt;/sup&gt;</td>
<td>750mg once followed by 500mg 12h later</td>
</tr>
<tr>
<td>Medication</td>
<td>Adult Dose</td>
</tr>
<tr>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>Alternatives</td>
<td>Halofantrine***</td>
</tr>
<tr>
<td>Chloroquine PLUS primaquine***</td>
<td>25 mg base/kg in 3 doses over 48h</td>
</tr>
<tr>
<td>PARENTERAL THERAPY: ALL PLASMODIA†</td>
<td>Quinidine gluconate</td>
</tr>
<tr>
<td>OR</td>
<td>Quinine dihydrochloride</td>
</tr>
<tr>
<td>Alternatives</td>
<td>Artemether***</td>
</tr>
<tr>
<td>PREVENTION OF RELAPSES (P. VIVAX AND P. OVALE ONLY)</td>
<td>Primaquine phosphate****</td>
</tr>
</tbody>
</table>

* Presumptive self-treatment of malaria is not routinely recommended; individuals with fever at risk of malaria should seek medical attention.
† Parenteral therapy should be used to treat individuals who are unable to take oral medications and those with severe or complicated malaria (i.e., malaria associated with impaired consciousness, coma, seizures, renal failure, pulmonary edema, shock, severe acidosis, severe jaundice, hypoglycemia, and/or parasitemia levels greater than 5–15%). Exchange transfusion has been helpful for some patients with high-density (>10%) parasitemia, altered mental status, pulmonary edema, or renal complications.
‡ Chloroquine-resistant *P. falciparum* has been reported in all malarious areas except Mexico, Central America west of the Panama Canal, Haiti, the Dominican Republic, and scattered areas of the Middle East. Chloroquine-resistant *P. vivax* has been reported in areas of Oceania including Indonesia, Papua–New Guinea, Vanuatu, and the Solomon Islands, as well as India, Thailand, Myanmar, and areas in South America, including Brazil, Guyana, and Peru.
§ If chloroquine phosphate is not available, hydroxychloroquine sulfate is equally effective; 400 mg of hydroxychloroquine sulfate salt is equivalent to 500 mg of chloroquine phosphate salt.
¶ Additional alternatives being actively studied for treatment of individuals with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* include artemether plus benflumetol (lumefantrine) (a combination is available as CGP 56697: co-artemether), pyronaridine, chlorproguanil plus dapsone, and chloroquine plus chlorpheniranine (see text). Multidrug-resistant *P. falciparum* (including resistance to mefloquine and halofantrine) has been reported in Southeast Asia, especially Thailand. A 7-day course of quinine...
and tetracycline or doxycycline can be used to treat individuals with *P. falciparum* acquired in these areas. Atovaquone plus proguanil also appears to be promising in early trials. Artesunate plus mefloquine, artemether plus mefloquine, and mefloquine plus tetracycline or doxycycline, have also been used to treat individuals infected with *multidrug-resistant P. falciparum*.

Fixed combination tablets of 250 mg atovaquone/100 mg proguanil and 62.5 mg atovaquone/25 mg proguanil are available in the United States. The combination should be used only in the treatment of individuals with malaria acquired in these areas. Atovaquone/proguanil may have certain advantages over other combination drugs. Due to high efficacy and a lower side effect profile, atovaquone/proguanil may have certain advantages over traditional quinine-based therapy in the treatment of such individuals. At present, atovaquone/proguanil should not be used in the treatment of pregnant women with malaria unless other agents are unavailable. Atovaquone/proguanil should not be used in the treatment of pregnant women with malaria unless other agents are unavailable. Atovaquone/proguanil should be used only for acute uncomplicated malaria caused by *P. falciparum*. Malaria caused by other agents may also be treated with this combination. Atovaquone/proguanil should be taken with food. The most common side effects are nausea, vomiting, and abdominal discomfort. The dose may be divided into the first day of therapy. Due to increasing tolerance to quinine in Southeast Asia, individuals with malaria acquired in these areas should be treated for 7 days if quinine is used. Quinine is usually poorly tolerated. Its use is associated with dizziness, tinnitus, deafness, and nausea. It may cause hypoglycemia and cardiac arrhythmias.††† Fixed combination Fansidar tablets contain 500 mg of sulfadoxine and 25 mg of pyrimethamine. Sulfadoxine-pyrimethamine resistance has been reported in Oceania, Sub-Saharan Africa, and the Amazon basin.‡‡‡ Safe to use in pregnant women and children.

§§§ Atovaquone/proguanil may be effective in clearing the erythrocytic phase of chloroquine-resistant *P. vivax*. Relapses may occur. Treatment failures and resistance have been reported, however, and the drug has caused that may affect the QT interval, such as quinine, quinidine, and mefloquine. Cardiac monitoring is recommended. Variability in absorption is a problem; halofantrine should not be taken one hour before to two hours after meals, because food increases its absorption. It should not be used in pregnancy.*** Not commercially available in the United States.
clearance of infection should be documented to exclude recrudescence of chloroquine-resistant organisms, especially chloroquine-resistant *P. falciparum* or *P. vivax* (31).

**Treatment of Chloroquine-Resistant Malaria**

**Quinine Sulfate and a Second Agent**  Quinine sulfate has historically been the agent of choice for treating individuals with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* or chloroquine-resistant *P. vivax* (31). This drug is, unfortunately, usually poorly tolerated, with patients reporting dizziness, tinnitus, deafness, and nausea. Quinine sulfate should be administered with a second agent, such as doxycycline or tetracycline in a nonpregnant adult, or clindamycin in pregnant women and children younger than 8 years of age (31,151–155). In some areas of the world, quinine sulfate is used with a one-time dose of sulfadoxine-pyrimethamine, although resistance to sulfadoxine-pyrimethamine limits the utility of this regimen (31). Increasing resistance to quinine has been reported in many areas, including Southeast Asia, South America, and Africa (24,106,156,157).

**Atovaquone and Proguanil**  The combination of atovaquone and proguanil is highly effective in the treatment of individuals with uncomplicated *P. falciparum* infection (158–163). In many areas of the world, combination atovaquone-proguanil is replacing quinine plus a second agent as the treatment of choice for individuals with uncomplicated malaria caused by *P. falciparum* (including chloroquine-resistant and multi-drug resistant strains). At therapeutic dosages, both agents are very well tolerated; the most frequently reported adverse events include mild abdominal discomfort with nausea, vomiting, diarrhea, and mild elevations in hepatic transaminases (160). Although the atovaquone–proguanil combination has not been extensively studied as a treatment for individuals with malaria caused by species other than *P. falciparum*, it has been uniformly effective in the small number of patients with *P. ovale*, *P. vivax*, and *P. malariae* infections in whom it has been used (134). When used to treat individuals with *P. vivax* or *P. ovale* infection, a subsequent course of primaquine must be administered to prevent late relapse (124,158).

**Atovaquone and Doxycycline**  A three-day course of oral atovaquone and doxycycline is also safe and effective in the treatment of individuals with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* (122,164). This combination should not be used in pregnant women and children younger than 8 years of age.

**Mefloquine**  Mefloquine became a drug of choice for the treatment of uncomplicated multidrug-resistant *P. falciparum* malaria in Southeast Asia in the 1980s (165). No parenteral formulation is available. Unfortunately, resistance has since appeared in Southeast Asia, especially in the border areas between Thailand and Cambodia and between Thailand and Myanmar (24,32). If mefloquine is used to treat individuals with malaria acquired in these areas, it should be used in combination with a second agent, usually an artemisinin derivative, tetracycline, or doxycycline (166,167). The drug should not be given with quinine, quinidine, or halofantrine (31). When mefloquine is used to treat individuals with malaria caused by chloroquine-resistant *P. falciparum* acquired along the border areas of Thailand or in the Amazon basin, a dosage of 25 mg/kg body weight should be used (24,31). When used in therapeutic dosages, this agent can precipitate anxiety attacks and other
neuropsychiatric adverse advents, including acute psychosis in as many as 1 in 250 to 1 in 1700 individuals (24,108).

**Halofantrine** Halofantrine is a phenanthrene methanol compound that is metabolized to its active form, desbutylhalofantrine, in vivo. This agent’s major use is in the treatment of individuals with multidrug-resistant *P. falciparum* infection. No parenteral formulation is available (108). Intestinal absorption can be variable and increases when the patient takes halofantrine with a fatty meal; because of its unpredictable absorption and toxicity, this drug should not be taken with food (31).

Halofantrine can prolong the PR and the corrected QT (QTc) intervals, resulting in ventricular arrhythmias (168). Due to a high incidence of cardiotoxicity, three-day regimens of this agent should not be employed. Even one-day regimens should not be administered to individuals with cardiac conduction abnormalities, and halofantrine should not be used to treat individuals taking other agents that affect the QT interval (such as mefloquine, quinidine, and quinine) (31).

**Artemisinin Derivatives** A number of artemisinin derivatives are in common use as antimalarial agents worldwide, including artemether, artesunate, and dihydroartemisinin. Artemisinin derivatives are the most rapidly acting of all malaria therapies (149). Preparations are available for oral, rectal (suppository), and parenteral administration. Unfortunately, all artemisinin derivatives can produce brain-stem damage in laboratory animals. The doses prescribed for humans are much lower than those causing toxicity in animals, however, and neuronal damage has not been observed in humans treated with these agents (108,169–172).

Artemisinin derivatives are most widely used for treating individuals infected with multidrug-resistant *P. falciparum* (173,174). Although clinical resistance to these drugs has not yet been described, reappearance of *P. falciparum* within 28 days of short (four- to five-day) courses of artemisinin derivatives limit the usefulness of these agents when used as monotherapy (175). As a consequence, they are often administered with a longer-acting agent, such as mefloquine or benflumetol (lumefantrine) (108,175–180).

**Co-artemether** Co-artemether (CGP 56697) is a 1:6 combination of short-acting artemether and long-acting benflumetol (lumefantrine). Lumefantrine is an arylamino alcohol schizonticide that bears certain structural similarities to quinine, mefloquine, and halofantrine; it appears to be less cardiotoxic than the latter agents (108,181,182).

Co-artemether is available in an oral preparation that is well tolerated (183). Absorption is variable, but increases with fatty foods (184,185). Co-artemether is effective in the treatment of individuals with uncomplicated chloroquine-resistant *P. falciparum* infection, although recrudescences occur when short-course therapy is used. To overcome this problem, a six-dose regimen (doses at 0, 8, 24, 48, 72, and 96 hours) is recommended (175,181,186,187).

**Pyronaridine** Pyronaridine is a benzonaphthyridine derivative that has been used in China for more than 20 years to treat individuals with malaria caused by *P. falciparum* or *P. vivax*. It is also being evaluated in the treatment of individuals infected with *P. ovale* or *P. malariae* (188). Pyronaridine is available in oral and parenteral formulations, is well tolerated, and is more effective than chloroquine in the treatment of partially immune individuals with uncomplicated malaria (189–191). Unfortunately, recrudescence rates as
high as 12% have been seen with pyronaridine monotherapy, especially in areas of South-

east Asia. In addition, increasing resistance is being recognized in areas of the world where

this agent has been widely used (192). A combination therapy consisting of pyronaridine

and sulfadoxine-pyrimethamine is now being evaluated (193).

**Chlorproguanil and Dapsone** Chlorproguanil is converted in vivo to chlorcycloguanil,

and the combination of chlorproguanil–dapsone potently inhibits folate synthesis (108).

This combination therapy is just as effective as treatment for individuals with uncompli-
cated *P. falciparum* infection as is sulfadoxine-pyrimethamine, and it is more effective than

chloroquine in areas characterized by chloroquine-resistant malaria (194–197). Some

strains of *P. falciparum* that are resistant to sulfadoxine-pyrimethamine are nevertheless

susceptible to chlorproguanil–dapsone (108,198). Unfortunately, strains that are resistant

to both chlorproguanil–dapsone and sulfadoxine-pyrimethamine have been identified in

Southeast Asia and are expected to spread (108).

The chlorproguanil–dapsone combination is administered orally and is well tolerated. At

present, it is primarily used as an inexpensive agent for the treatment of uncomplicated

*P. falciparum* infection in areas of Africa where sulfadoxine-pyrimethamine is no longer

effective.

**Chloroquine and Chlorpheniramine** Chlorpheniramine is a histamine H₁ receptor

antagonist. Simultaneous administration of chlorpheniramine and chloroquine increases

whole-blood chloroquine concentrations in vivo (through an unclear mechanism), result-
ing in a limited “reversal” of chloroquine resistance (108,199). In field studies in West

Africa, the chloroquine–chlorpheniramine combination appeared to be more effective than

either chloroquine alone or sulfadoxine-pyrimethamine in treating individuals with uncom-
plicated *P. falciparum* malaria, but less effective than mefloquine (the protective efficacy

of chloroquine–chlorpheniramine in this setting is 65% to 100%) (199–203). Whether the

combination offers similar effectiveness outside of West Africa remains unknown. The drug

combination is, however, well tolerated (202,203).

**Treatment of Multidrug-Resistant *P. falciparum***

The optimal treatment for uncomplicated, multidrug-resistant *P. falciparum* infection

(including resistance to chloroquine, mefloquine, sulfadoxine-pyrimethamine, and
tolerance to quinine) has not yet been established. Atovaquone-proguanil combination

therapy shows promise. Other currently used regimens include seven-day courses of

quinine with tetracycline or doxycycline; mefloquine–artesunate combination therapy;
mefloquine–artemether combination therapy; and combination therapy with mefloquine

and either tetracycline or doxycycline (31,163,166).

**Treatment of Chloroquine-Resistant *P. vivax***

Although formal efficacy studies have not been performed, current therapy for chloroquine-

resistant *P. vivax* infection resembles that for chloroquine-resistant *P. falciparum* infection.

Quinine sulfate with a second agent such as doxycycline or sulfadoxine-pyrimethamine

may be administered (31). Individuals with chloroquine-resistant *P. vivax* have also been

successfully treated with therapeutic doses of mefloquine or halofantrine as well as com-
bination therapy with chloroquine and primaquine (137). If combination atovaquone-

proguanil is used, terminal treatment with primaquine is required.
Parenteral Therapy for Severe/Complicated Malaria

Parenteral therapy should be used to treat individuals with severe or complicated malaria—that is, malaria associated with impaired consciousness, coma, seizures, renal failure, pulmonary edema, shock, severe acidosis, severe jaundice, hypoglycemia, and/or parasitemia levels greater than 5% to 15% (2,149,150). In addition, it is recommended for individuals with malaria who cannot take oral medications.

Quinidine Gluconate and Quinine Dihydrochloride  In many areas of the world, quinine dihydrochloride is the parenteral agent of choice for treating individuals with severe malaria. In the United States, parenteral quinine is not available; quinidine gluconate is used instead. The latter agent is more active than quinine against malaria, but it is also more expensive and more cardiotoxic (204–207).

Quinine dihydrochloride may be administered intravenously or intramuscularly. Quinidine gluconate, a class IA antiarrhythmic agent, should be administered intravenously. Both intravenous quinidine and quinine should be delivered by continuous infusion; when they are administered by rapid or bolus injection, they can induce fatal hypotension (31,149). Individuals receiving parenteral quinidine should be monitored electrocardiographically. If the QTc interval increases more than 25% above the baseline reading, then the infusion rate should be reduced.

Intravenous therapy with quinine or quinidine should continue until the patient is able to take oral medications. If parenteral therapy extends over more than two or three days, the intravenous dose should be reduced by 30% to 50% after 48 to 72 hours to avoid accumulation of drugs and increased toxicity (31,149). The intravenous administration of quinine or quinidine can induce hypoglycemia, which usually occurs 24 hours after treatment is initiated and most frequently affects pregnant women and small children (31,149,208).

Artemisinin Derivatives  Parenteral artemether has also been used in the treatment of individuals with severe malaria. Clinicians originally hoped that the ability of these drugs to rapidly clear parasitemia would decrease mortality associated with severe malaria. Unfortunately, artemisinin derivatives do not appear to be more effective than quinine in this respect, although they do offer equivalent performance (149,209–211). Artemisinin derivatives can be given via rectal suppository if parenteral therapy is unavailable (212).

Prevention of Relapses

The liver hypnozoite stages of *P. vivax* and *P. ovale* can lead to relapses months or even years after the individual originally became infected. To prevent late relapses, patients with *P. vivax* or *P. ovale* infection should receive primaquine. This drug should not be used in pregnant women and in individuals deficient in glucose 6-phosphate dehydrogenase. Strains of *P. vivax* that are tolerant (or even resistant) to primaquine have been reported in areas of Southeast Asia and East Africa (including Somalia); larger doses of primaquine should be used to treat individuals with such strains (213–215).

Treatment of Malaria During Pregnancy

Malaria during pregnancy represents a life-threatening infection for both mother and fetus. Therapy should therefore be directed toward eradicating infection. The susceptibility to malaria is highest during the second and third trimesters of pregnancy and the early postpartum period (up to 60 days after delivery) (216).
Chloroquine is safe for use in this patient population. When appropriately administered, quinine or quinidine with clindamycin is also safe, although hypoglycemia and hypotension can complicate the administration of parenteral quinine and quinidine during pregnancy. Doxycycline, primaquine, and tafenoquine should not be used. Treatment with mefloquine of pregnant women with malaria may increase the risk of stillbirth; until further evaluations are performed, treatment-dose mefloquine should not be administered during pregnancy unless other agents prove insufficient or are unavailable (217). Halofantrine is toxic to embryos in animal studies and should not be used during pregnancy (109). Although sulfadoxine-pyrimethamine is considered safe during all trimesters of pregnancy, sulfadoxine may cause kernicterus if given during the third trimester. Although artemisinin derivatives have been used with apparent safety in the second and third trimesters of pregnancy, they can cause resorption of embryos in animal studies; consequently, these agents should not be used during the first trimester (110,218). As yet, insufficient data have been gathered to prove or disprove the safety during pregnancy of artemether–benflumetol (lumefantrine), pyronaridine, chlorproguanil–dapsone, chloroquine–chlorpheniramine, and combination atovaquone-proguanil.

Ancillary Treatment

Few ancillary therapies have been shown to be effective in the treatment of individuals with malaria (2,150). Antipyretics can lower fever, and intravenous administration of glucose-containing solution may lessen the incidence of hypoglycemia (149). Exchange transfusions can benefit individuals with severe or complicated malaria with parasitemia levels exceeding 5% to 15% (219,220).

Steroids, heparin, and cyclosporin do not offer benefits in the treatment of individuals with malaria (149). Likewise, the administration of iron chelators (such as deferoxamine), antitumor necrosis factor agents (such as pentoxifylline), and agents that lower intracranial pressure (such as mannitol) has not been shown to help individuals with malaria (221–224).

Although prophylactic use of antiseizure medications such as phenobarbital does prevent seizures in individuals with cerebral malaria, administration of such agents also doubles the mortality rate due to respiratory arrests in such individuals. Consequently, individuals with malaria receiving prophylactic phenobarbital should be carefully monitored (225).

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REFERENCES


57 Clark IA, Cowden WB. Why is the pathology of falciparum worse than that of vivax malaria? Parasitol Today 1999;15:458–461.

Malaria: Epidemiology, Pathogenesis, Diagnosis, Prevention, and Treatment


112 Lobel HO, Kozarsky PE. Update on prevention of malaria for travelers [see comments]. JAMA 1997;278:1767–1771.


