albimanus, Anopheles quadrimaculatus, and *Anopheles freeborni*) that remain common in the United States.[318,319] "Airport malaria" occurs when infected mosquitoes arrive from an endemic country on an aircraft from which they escape to bite local residents.[320] Because mosquitoes travel short distances, infections of local residents tend to occur near airports.[321] The spraying of insecticide within aircraft leaving endemic areas reduces the incidence of airport malaria.[322] Malaria may also be acquired from needles shared among drug users, blood transfusion,[323,324] or solid-organ transplantation.[325] These blood and organ donors are usually asymptomatic persons from endemic areas with low-level parasitemia. The incidence of transfusion-acquired malaria is reduced when returned travelers and former residents of malaria-endemic areas are required to wait 1 and 3 years, respectively, before donating blood.[323] Malaria may also be acquired congenitally.[326]

DISTRIBUTION OF DRUG RESISTANCE

The widespread and complicated patterns of *P. falciparum* resistance to antimalarials has resulted in various ACT regimens becoming the first- or second-line drug regimens in most of the world's malaria-endemic countries (see Fig. 274.6).

Chloroquine-resistant *P. falciparum* malaria is widespread in sub-Saharan Africa, Asia, and Latin America. It has also been reported in areas of the Middle East, including Iran, Yemen, Oman, and Saudi Arabia,[327–331] but not in Mexico, other regions of Central America west of the Panama Canal, Haiti, or the Dominican Republic. High-grade resistance of *P. vivax* malaria to chloroquine has been reported in Papua New Guinea and Indonesia.[332–334] Case reports of *P. vivax* malaria not responsive to chloroquine treatment have also been reported from India, Myanmar, and Central and South America.[335–340] Chloroquine-resistant *P. malariae* has been reported in Sumatra, Indonesia.[341] In some regions of Africa and China where chloroquine availability has ceased, chloroquine-sensitive *P. falciparum* strains have gradually returned to a greater prevalence.[342–347]

Amodiaquine-resistant *P. falciparum* has been reported in several regions of Africa[348–352] and Asia.[353,354] Mefloquine-resistant *P. falciparum* malaria now occurs along the various border regions of Thailand, Myanmar, southern China, Cambodia, Laos, and Vietnam,[355–357] with scattered cases reported in the Amazon Basin[358] and Africa.[359]

Resistance to sulfadoxine-pyrimethamine (SP) is widespread through much of Southeast Asia,[360–362] the Amazon Basin,[363,364] and Africa.[365–367] The prevalence of SP resistance varies among African regions, with some areas of West Africa showing relatively low rates of resistance.[368] Malaria strains resistant to cycloguanil (the active metabolite of proguanil) have been reported since the late 1940s[369–371] and can exhibit different degrees of cross-resistance to pyrimethamine.[372,373] Interindividual variations of conversion to cycloguanil may also contribute to clinical success or failure of proguanil treatment.[374–376]

Resistance to atovaquone-proguanil was previously reported only with its use in prophylaxis, but with increasing use for the treatment of uncomplicated malaria, frank treatment failures have been reported from several countries.[377–381] Reduced susceptibility to quinine has been reported mostly in Southeast Asia[382] but also in sub-Saharan Africa and South America.[383,384]

Concerns about the emergence of resistance to artemisinin derivatives were first raised with reports of treatment failures with artesunate-mefloquine and artemether-lumefantrine in Thai and Cambodian malaria control programs.[385,392] These failures may be associated with slow parasite clearance rates in response to artemisinin derivatives in vivo, which have now been carefully documented in Cambodia,[386–388] Thailand,[389] Vietnam,[390] Myanmar, Laos, and southern China (see Fig. 274.6).[391–393] These findings have invoked the specter of current ACT regimens becoming less effective throughout Southeast Asia, prompting WHO to launch a "Global Plan for Artemisinin Resistance Containment" in 2011 and an "Emergency Response to Artemisinin Resistance in the Greater Mekong Subregion" in 2013.[394,395] These observations have also raised the possibility that rapid parasite clearance, a hallmark benefit of artemisinins in the treatment of severe malaria, may become less dependable after artemisinin dosing in this region.[396]

ANTIMALARIAL DRUGS: MECHANISMS OF ACTION AND RESISTANCE

Chloroquine

Intraerythrocytic parasites consume the hemoglobin of their host cells, breaking it down within a large digestive vacuole (see Fig. 274.4B) and releasing heme molecules that are poisonous if not detoxified. Malaria parasites normally allow these heme molecules to polymerize into inert crystals called hemozoin, which can be visualized by light microscopy as intraerythrocytic pigment in thin blood smears (Fig. 274.7E and H). Chloroquine acts by forming toxic complexes with heme molecules and interfering with their crystallization.[397] This mechanism of action explains why chloroquine is effective against developing intraerythrocytic trophozoites but ineffective against other parasite stages (i.e., mature gametocytes, liver schizonts) that do not actively consume hemoglobin.

Chloroquine-resistant *P. falciparum* parasites reduce the amount of drug that accumulates in their digestive vacuoles.[398] The mechanism involves mutations in a conserved transport molecule of the digestive vacuole membrane known as *P. falciparum* chloroquine resistance transporter (PfCRT).[399–401] Evidence indicates that the mutated PfCRT molecule functions as a saturable simple carrier under the influence of an electrochemical gradient[402,403] and that a specific interaction between chloroquine and the modified form of PfCRT[400] is involved in the facilitated diffusion of chloroquine from the digestive vacuole.[404–406] The *pfcrt* mutations responsible for chloroquine resistance include a key change from lysine to threonine in the 76th amino acid (K76T) plus additional mutations that depend on their geographic origin.[399,407–409] Drug selection for mutant PfCRT is evident in the association of the K76T marker with increased plasma chloroquine levels[410] and with treatment failures in children receiving the drug.[411]

Although PfCRT is the central determinant of chloroquine resistance, other host and parasite factors also influence treatment outcomes. For example, clearance of phenotypically chloroquine-resistant parasites can occur after chloroquine treatment and becomes increasingly prevalent in children as they grow older, presumably because of the immunity that develops from repeated episodes of malaria.[411,412] Parasite transport molecules in addition to PfCRT have also been proposed to modulate or contribute to the ability of chloroquine-resistant parasites to cope with the drug.[413,414]

Amodiaquine

Amodiaquine, a 4-aminoquinoline compound related to chloroquine, is often used successfully against chloroquine-resistant strains of *P. falciparum* in Africa, but it is largely ineffective in South America. The resistance profiles responsible for these different responses are attributable to the particular histories of drug selection pressure in Africa or South America, and the evolution of distinct suites of mutations in *pfcrt* and *pfmdr1,* the *P. falciparum* multidrug resistance gene 1 encoding P-glycoprotein homologue-1.[415]

Piperaquine

Piperaquine, a *bis*-aminoquinoline compound related to chloroquine, is used widely as a partner drug in artemisinin-based combination therapy in Southeast Asia and Africa. Resistance to piperaquine has recently emerged in Cambodia,[416] where it has been associated with emerging mutations of the *pfcrt* gene[417] as well as amplifications of the *plasmepsin 2* and *plasmepsin 3* genes[418,419] that encode aspartic proteases involved in hemoglobin digestion. The role of these enzymes in conferring piperaquine resistance is under investigation.

Sulfadoxine-Pyrimethamine

Dihydropteroate synthase (DHPS) and dihydrofolate reductase (DHFR) are sequentially involved in the folate pathway of nucleic acid synthesis. Pyrimethamine inhibits parasite DHFR activity and the production of tetrahydrofolate, an essential cofactor for one-carbon metabolism required for the synthesis of nucleic acids and certain amino acids. Point mutations in DHFR reduce its affinity for pyrimethamine. The substitution of asparagine for serine at position 108 in DHFR is critical for the initial development of pyrimethamine resistance, with additional mutations (Ile51, Arg59, Leu164) increasing the degree of pyrimethamine

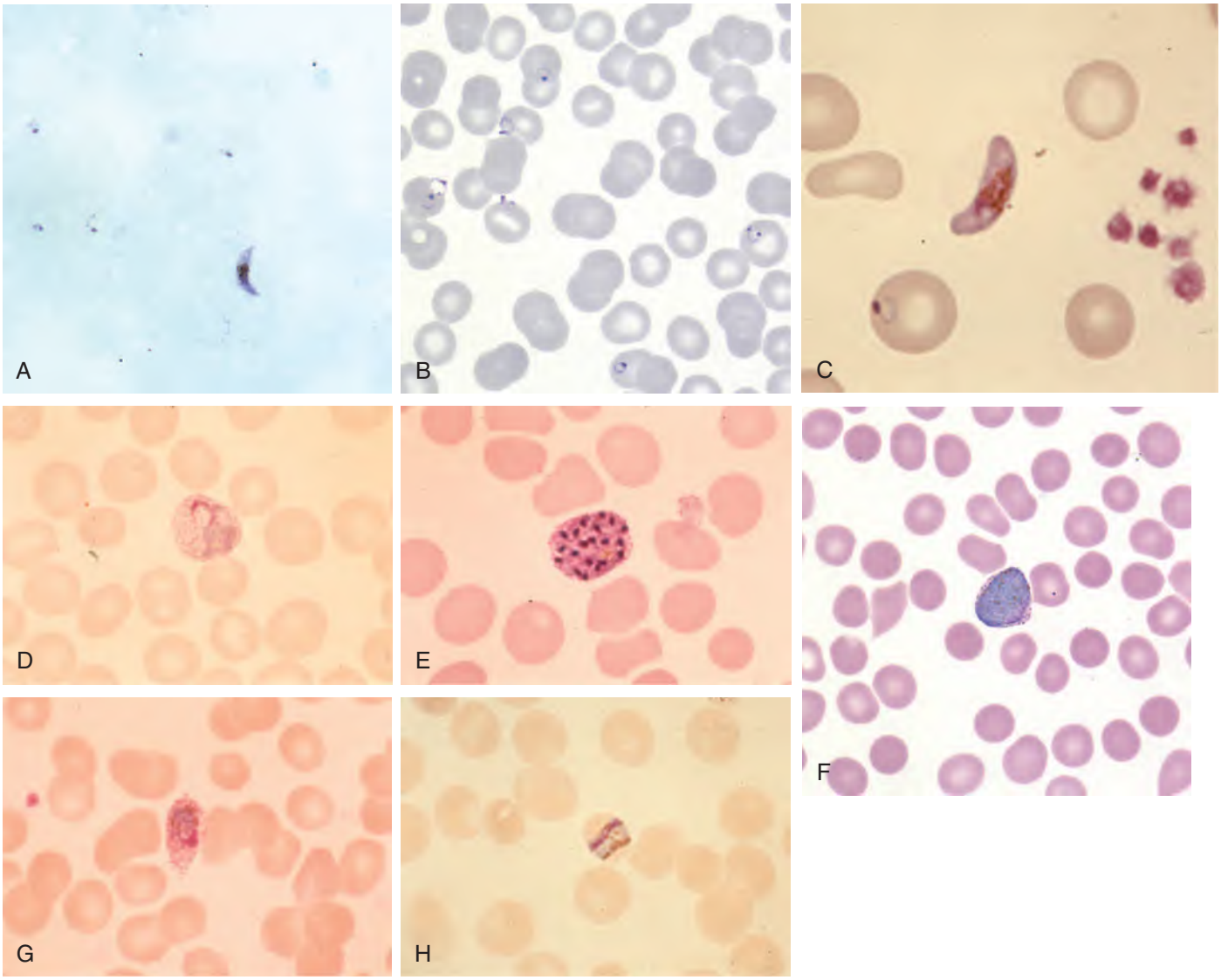

FIG. 274.7 Giemsa-stained thick (A) and thin (B–H) smears used for the diagnosis of malaria and the speciation of *Plasmodium* parasites. (A) Multiple signet-ring *P. falciparum* trophozoites, which are visualized outside erythrocytes in thick blood smear preparations. (B) A multiply infected erythrocyte containing signet-ring *P. falciparum* trophozoites, including an accolade form positioned up against the inner surface of the erythrocyte membrane in fixed thin blood smear preparations. (C) Banana-shaped gametocyte unique to *P. falciparum*. (D) Ameboid trophozoite characteristic of *P. vivax*. Both *P. vivax*– and *P. ovale*–infected erythrocytes exhibit Schuffner dots and tend to be enlarged compared with uninfected erythrocytes. (E) *P. vivax* schizont. Mature *P. falciparum* parasites, by contrast, are rarely seen on blood smears because they sequester in the systemic microvasculature. (F) *P. vivax* spherical gametocyte. (G) *P. ovale* trophozoite. Note Schuffner dots and ovoid shape of the infected erythrocyte. (H) Characteristic band form trophozoite of *P. malariae* containing intracellular pigment hemozoin. *(A, B, and F courtesy DPDx - Laboratory Identification of Parasites of Public Health Concern [the CDC's website for parasitology identification] at* https://www.cdc.gov/dpdx/index.html. *C, D, E, G, and H courtesy David Wyler, Newton, MA.)*

resistance.[420,421] Part of sulfadoxine's action is thought to be inhibition of parasite DHPS, and point mutations in DHPS reduce its affinity for sulfadoxine.[422,423] Analysis of the mutant *dhfr* and *dhps* alleles in field studies supports conclusions that clinically significant resistance to pyrimethamine arises from multiple mutations in *dhfr* and *dhps* and that *dhps* mutations are likely selected after mutations in *dhfr* are already present.[424]

Atovaquone-Proguanil (Malarone)

Atovaquone binds cytochrome *b* and inhibits parasite mitochondrial proton transport, leading to collapse of the mitochondrial membrane potential.[425,426] This effect is potentiated by proguanil.[427] The substitution of serine for tyrosine at codon 268 of the cytochrome *b* gene is associated with resistance to atovaquone and the atovaquone-proguanil (Malarone) combination.[378,379,428,429] Cycloguanil, the active metabolite of proguanil, inhibits DHFR.[430] Point mutations in *dhfr* confer resistance to cycloguanil.[374,375,431,432]

Doxycycline

Doxycycline inhibits protein synthesis elongation by preventing binding of aminoacyl–transfer RNA to the ribosome 30S subunit. Resistance of human malaria parasites to this drug has not been described.

Mefloquine, Quinidine, Quinine

Mefloquine, quinidine, and quinine are thought to form complexes toxic to the parasite by binding to heme and inhibiting its polymerization.[433,434] Mefloquine resistance may be associated in part with increases in expression and mutations in *pfmdr1*.[413,435,436] Decreased quinine susceptibility is associated with resistance to other structurally related drugs such as mefloquine and halofantrine, suggesting that drug resistance mechanisms may share various genetic determinants.[437–439] Some studies have implicated *pfmdr1* mutations in mefloquine, quinine, and halofantrine resistance and *pfcrt* mutations in quinine and quinidine responses.[400,401,413,440,441] The different levels of quinine susceptibility among parasites and the relatively slow rate at which quinine resistance

has spread throughout the world indicate that quinine resistance is a complex phenotype and is probably affected by other genes in addition to *pfmdr1* and *pfcrt*. The results of a linkage analysis and surveys of parasites from Southeast Asia, Africa, and South America support a model in which multiple genes can combine in different ways to produce similar phenotypes of reduced quinine response.[414,441]

Artemisinin Derivatives

In original studies of artemisinin treatment responses in humans, frequent recrudescences were observed after 3-, 5-, and 7-day regimens of monotherapy.[442,443] This inherent resistance of *P. falciparum* (Rl level by WHO definition)[444] led to an early recommendation that artemisinin always be used with partner drugs in combination therapy.[443] Although high-level resistance to artemisinin derivatives has not been found in clinical samples, successful selection of rodent malaria parasite strains with reduced susceptibility[445,446] and reports of *P. falciparum* strains with slow clearance rates in vivo[396] initially raised concerns that strains of human malaria parasites with significant clinical resistance may evolve and spread. Indeed, artemisinin resistance,[447,448] defined as a slow parasite clearance half-life in patients receiving an artemisinin derivative, has been reported extensively from Cambodia,[386–388] Thailand,[389] Vietnam,[390] Myanmar, Laos, and southern China.[386–391,449–451] Multiple single nucleotide polymorphisms in the propeller domain of the *P. falciparum* kelch13 (K13) protein have been associated with slow clearance half-life in Cambodia,[452–454] although exceptions are reported[455,456] and immunity has been shown to have an important effect on the clearance phenotype.[457] These single nucleotide polymorphisms have arisen independently and are linked to decreased susceptibility of young (0–3 hours old) ring-stage parasites to a pharmacologically relevant exposure to artemisinin in vitro.[452,458] Genome-wide association studies of parasite subpopulations in Western Cambodia[459,460] have suggested that the genetic determinants of artemisinin response may involve multiple genes, including *pfcrt, pfmdr2, arps10,* and *fd*.[460,461]

Artemisinin-resistant ring-stage parasites were recently found to have increased expression of the unfolded protein response pathway, which is proposed to mitigate the protein damage caused by artemisinin.[462] Apart from this ring-stage phenotype, a dormancy phenotype has been proposed for the clinical recrudescences inherent to *P. falciparum* infection.[463,464] Recent studies suggest that parasite dormancy may involve integrated stress response pathways and global inhibition of protein synthesis through phosphorylation of *Plasmodium* eukaryotic initiation factor 2α, leading to a protective latent state.[465]

In sub-Saharan Africa fast parasite clearance half-lives predominate after ACT treatment, despite the finding of K13 propeller mutations at low prevalence.[466–469] This difference may be attributed to the absence of the "genetic background" mutations found in Southeast Asia.[468] Natural factors of resistance and acquired immunity from greater exposure to malaria could also be responsible for major differences in clearance rates.[469]

CLINICAL PRESENTATION AND DIAGNOSIS OF MALARIA

The malaria incubation period after an infective mosquito bite includes the time required for the parasites to progress through liver schizogony and produce symptoms by their propagation in the bloodstream. For primary attacks, this period is typically about 8 to 25 days but may be much longer, depending on the immune status of the infected person, the strain as well as the species of *Plasmodium,* the dose of sporozoites, and the possible effects of partially effective chemoprophylaxis. Relapses from latent hypnozoites (*P. vivax, P. ovale*) may develop months or years after mosquito bites. Late-onset or recrudescent *P. falciparum* malaria may also occur in individuals who have suppressed the parasitemia of drug-resistant parasites with chemoprophylactic drugs[470] (see Fig. 274.2). Febrile patients presenting within 7 days of entering an endemic area are unlikely to have malaria, unless there has been earlier exposure to infective mosquito bites. As a general rule, and because of the dangers of acute *P. falciparum* infection, all travelers who have visited a malaria-endemic area in the 3 months before onset of fever or other suggestive symptoms should be considered to have malaria until proven otherwise. Even in patients beyond this time frame, it is wise to consider *P. falciparum* malaria, as illustrated, for example, in the report of a symptomatic presentation in an 18-year-old patient with sickle cell disease 4 years after visiting an endemic area.[299] Latent attacks from the reactivation of *P. vivax* or *P. ovale* hypnozoites usually occur within 3 years and are rare more than 5 years after exposure. Recrudescence of *P. malariae* symptoms in individuals with subclinical parasitemia has been reported decades after initial infection.[200,471,472]

History and Physical Examination

Uncomplicated malaria typically presents as an undifferentiated febrile illness.[473] A series of 160 German nationals or residents with imported malaria presented to a travel clinic with the following symptoms: fever (100%); headache (100%); weakness (94%); profuse night sweats (91%); insomnia (69%); arthralgias (59%); myalgias (56%); diarrhea (13%); and abdominal cramps (8%).[474] The bloodstream parasites of *P. falciparum* infections are often asynchronous and may produce continuous fever. In other infections, fever can recur in a pattern that depends on the synchrony of the replicating parasites, and whether mixed subpopulations of parasites (possibly including mixed *Plasmodium* species) are on different cycles in the bloodstream. Patients with cyclic fevers may be relatively asymptomatic during afebrile periods.

Signal elements from the history and physical examination, when considered together, may be suggestive of the diagnosis of malaria.[475–477] Cyclic paroxysms of chills and rigors, fever, and drenching sweats are characteristic although not necessarily specific for malaria. A travel history that reveals risk of exposure months to years before in an endemic region is an alert for malaria and should always be sought in presentations of fever. Findings on physical examination may include pallor and hepatosplenomegaly. Rarely, acute *Plasmodium* infections present with splenic rupture requiring surgery or conservative management.[478,479] Findings such as jaundice, diminished consciousness, or convulsions indicate severe malaria (see "Severe *P. falciparum* Malaria" later). Rash, lymphadenopathy, and signs of pulmonary consolidation are distinctly uncommon.

Thick and Thin Blood Smears

Light microscopy of Giemsa-stained blood smears is the accepted standard for malaria diagnosis. Thick and thin diagnostic blood smears should be *prepared and read immediately by experienced personnel* when the clinical presentation and travel history are compatible with malaria.[480] Preparation instructions and representative images from thick and thin smears are available from the CDC's website for parasitologic diagnosis: DPDx - Laboratory Identification of Parasites of Public Health Concern (https://www.cdc.gov/dpdx/index.html).

Thick smears concentrate red cell layers approximately 40-fold and are used to screen a relatively large amount of blood for the presence of parasites. Because erythrocytes are lysed in the process of staining in the thick smear technique, parasites are visualized *outside* red cells (see Fig. 274.7A). Assuming an average white cell count of 8000/μL, parasitemia can be estimated from a thick smear by counting the number of parasites until 200 white cells have also been counted. This count, when multiplied by 40, gives an indication of the number of parasites per microliter of blood. The parasitemia percentage can then be calculated by dividing the parasite density by 4,000,000 (the average number of erythrocytes per microliter in blood) and multiplying by 100.

Parasite density can be associated with disease severity and must be monitored during and after treatment to ensure adequate resolution of infection. Detectable parasitemia may lag behind aches, fevers, and chills, sometimes for many days; individuals with no antimalarial immunity may have severe manifestations of malaria even though parasites are very difficult to detect on blood smear. A *P. falciparum* infection also may not be apparent on an initial blood smear if the parasites are predominantly mature cytoadherent forms (i.e., trophozoite- and schizont-infected erythrocytes) and are sequestered in the microvasculature. Therefore if the initial blood smear is negative and malaria remains possible, the smear should be repeated every 12 hours until a diagnosis of malaria is made or ruled out. Before reading a thick blood smear as negative, at least 200 to 500 fields should be examined at a magnification of 1000× with an oil immersion objective lens; some experts recommend examining a thick smear for 20 minutes. Blood smear–confirmed (or polymerase chain reaction–confirmed) malaria

is a nationally notifiable disease in the United States; typically, such cases are reported by health care providers or laboratories to their local or state health departments and then to the CDC. The CDC has requested that a pretreatment whole blood sample (in ethylenediaminetetraacetic acid anticoagulant) be submitted for all cases diagnosed in the United States for species confirmation and drug resistance surveillance. Details on how to report a case using the CDC's Malaria Case Surveillance Form and how to ship blood specimens using the CDC's Specimen Submission Form are provided at the CDC's malaria website (https://www.cdc.gov/malaria/report.html).

Giemsa-stained thin smears are prepared from a much smaller amount of blood than thick smears and are used to determine the *Plasmodium* species (see Fig. 274.7B to H). Speciation of malaria parasites has important implications for treatment. *P. falciparum* infections are characterized by thin delicate rings that may be positioned at the membrane of the red cell (so-called accolade forms) (see Fig. 274.7B), multiply infected cells containing signet-ring forms (see Fig. 274.7B), *absence* of trophozoites and schizonts because they are sequestered in the microvasculature, and banana-shaped gametocytes (see Fig. 274.7C). *P. vivax* and *P. ovale* are characterized by relatively thicker rings, ameboid trophozoites (see Fig. 274.7D), schizonts (see Fig. 274.7E) in the peripheral blood, and spherically shaped gametocytes (see Fig. 274.7F). Erythrocyte enlargement and Schuffner dots (see Fig. 274.7D and G) are common features of *P. vivax* and *P. ovale,* but not *P. falciparum* or *P. malariae. P. malariae* can be distinguished by its band forms, if present (see Fig. 274.7H). On blood smear examination, ring forms of *P. knowlesi* are indistinguishable from those of *P. falciparum,* and mature forms and gametocytes are indistinguishable from those of *P. malariae.*[17,308,481] Thin-smear examination can yield additional useful information, such as the presence of intraleukocytic pigment (a poor prognostic sign)[482] or other blood pathogens (e.g., filaria, *Borrelia recurrentis*). *Babesia* species produce intraerythrocytic forms that may be confused with *Plasmodium* species,[483] but experienced personnel are able to distinguish between them.

Rapid Diagnostic Tests

Although evaluation of Giemsa-stained thick and thin smears remains the accepted standard for malaria diagnosis, rapid diagnostic tests (RDTs) have become increasingly useful.[484–490] In situations in which expert microscopic examination is delayed or difficult to obtain, medical decisions and management of malaria cases can benefit greatly from the appropriate use of RDTs. In US health care settings, the CDC recommends that all positive and negative RDT results be confirmed by microscopy, which can provide additional information on species, life-cycle stages, and level of parasitemia that may be useful in clinical management. Two types of RDTs based on different detection schemes are presently available and are becoming more frequently used.

The first type is based on the detection of *Plasmodium* histidine-rich protein-2 (HRP-2).[491] In 556 travelers returning to France with suspected malaria, a US Food and Drug Administration (FDA)–approved commercial test based on HRP-2 had 96% sensitivity and 99% specificity for *Plasmodium* infection when compared with microscopy.[492] In 32 US marines returning from Liberia with febrile illness, this test had a 100% sensitivity and a 100% specificity for *P. falciparum* infection when compared with microscopy.[493] Although HRP-2 tests are highly sensitive and specific for malaria diagnosis, they have certain limitations. First, HRP-2–based detection is limited to *P. falciparum* and may yield negative results in cases in which the *P. falciparum* strain either does not express HRP-2 antigen[494–497] or produces a test-interfering prozone effect.[498,499] Other antigen detection schemes are required for *P. vivax, P. ovale,* and *P. malariae.* These are generally less sensitive than is HRP-2 detection for *P. falciparum*,[492,500] making them less useful for the diagnosis of malaria in returned travelers, who typically are infected with *P. vivax* at least as often as with *P. falciparum.* Second, HRP-2 tests are of limited use in monitoring therapeutic responses because the tests are persistently positive up to 28 days after treatment. Third, the sensitivity of many rapid detection tests for *P. falciparum* and *P. vivax* infections drops at parasite densities of less than 100 to 1000/μL,[500] making them less useful for the diagnosis of malaria in nonimmune returned travelers, who may experience symptoms of malaria at low parasite densities. A recently improved HRP-2–based RDT format may improve the detection of *P. falciparum* infection as much as 10-fold.[501,502] WHO provides a list of prequalified malaria RDT products and manufacturers (https://www.who.int/diagnostics_laboratory/evaluations/190527_prequalified_product_list.pdf?ua/=1). In the United States, the BinaxNOW Malaria test (Abbott, Abbott Park, IL) is FDA approved for use by hospital and commercial laboratories, but not clinicians or patients (https://www.cdc.gov/malaria/diagnosis_treatment/diagnostic_tools.html).

The second type of RDT is based on detection of *P. falciparum*–specific lactate dehydrogenase (LDH) and pan-*Plasmodium* LDH.[503] In 556 travelers returning to France with suspected malaria, a parasite LDH test had 80% sensitivity and 98% specificity for *Plasmodium* infection when compared with microscopy.[492] Parasite LDH tests commonly detect *P. vivax, P. ovale,* and *P. malariae* with less sensitivity than *P. falciparum* relative to expert microscopy.[492,504,505] For example, only 3 of 12 (25%) *P. ovale* infections tested positive in French peacekeepers returning from Côte d'Ivoire with malaria.[506] A parasite LDH RDT has a lower sensitivity for *P. falciparum* and *P. vivax* infections when parasite densities are less than 100 to 1000/μL.[507] An advantage to parasite LDH detection is that the signal is proportional to *P. falciparum* parasitemia,[508] allowing for monitoring of therapeutic responses. Although this test is commercially available worldwide, it is currently provided only for research purposes in the United States.

A combination *P. falciparum* HRP-2/LDH test, which takes advantage of the lower limit of HRP-2 detection relative to LDH and can still detect blood parasitemia in the event of no HRP-2 expression or a prozone effect, is under evaluation.[509]

Other Laboratory Tests

The results of routine clinical laboratory tests are not specific for malaria but may support its diagnosis. Some degree of anemia may be seen with malaria from all *Plasmodium* species. Decreases in hemoglobin, hematocrit, and haptoglobin and increases in lactic acid dehydrogenase may be marked with large *P. falciparum* parasite burdens. Microcytosis may be seen in patients from malaria-endemic areas but is often due to iron deficiency or thalassemia. Leukocyte counts may be high, normal, or low.[510] Platelet counts may be normal or slightly low[511] but have been observed to be less than 70,000/μL in *P. falciparum* infection[512] and occasionally in *P. vivax* infection.[513] Sodium may be slightly low, possibly because of the syndrome of inappropriate antidiuretic hormone, excessive vomiting, or urinary losses.[514] Acidemia (pH <7.35), acidosis (bicarbonate <15 mmol/L), and lactate levels greater than 5 mmol/L can be seen in severe *P. falciparum* malaria. Some degree of renal impairment is common in falciparum malaria and may be associated with increased creatinine, proteinuria, and hemoglobinuria.[515] Serum glucose is often low in children with *P. falciparum* malaria, but it is commonly normal in adults. In African children with severe *P. falciparum* malaria, bacteremia/sepsis may be present at the time of initial clinical evaluation and blood cultures may be positive.[52,516] This finding is much less common in adults with imported severe malaria.[517]

Severe *P. falciparum* Malaria

WHO has established clinical and laboratory criteria for severe *P. falciparum* malaria, which must be treated as an emergency requiring intensive medical care.[518] Severe malaria is established by any of the criteria in Table 274.1 in the presence of *P. falciparum* parasitemia and with reasonable exclusion of an alternative diagnosis. Although these WHO criteria are largely based on the clinical presentation of severe malaria among young African children living in endemic areas,[62] they are consistent with the clinical spectrum of severe malaria in travelers who might be encountered in nonendemic developed countries.[516,519] Nonimmune individuals who do not meet these criteria for severe malaria should be treated initially with antimalarial drugs as if they have it. In practice, because of the ability of *P. falciparum* infection to progress in just a few hours to severe and life-threatening complications, it is advisable to hospitalize all nonimmune individuals during their initial period of treatment. If blood smears or RDTs are negative but severe malaria is strongly suspected, patients should be treated for severe malaria, while repeated thick smears and tests for other possible diseases should be pursued for a definitive diagnosis.

TABLE 274.1 Diagnostic Features of Severe Malaria

Cerebral malaria (diminished consciousness, seizures)
Respiratory distress
Prostration
Hyperparasitemia
Severe anemia
Hypoglycemia
Jaundice/icterus
Renal insufficiency
Hemoglobinuria
Shock
Cessation of eating and drinking
Repetitive vomiting
Hyperpyrexia

TABLE 274.2 Differential Diagnosis of the Malaria Presentation: Selected Examples

Influenza
Enteric fever
Bacteremia/sepsis
Classic dengue fever
Acute schistosomiasis (Katayama fever)
Leptospirosis
African tick fever
East African trypanosomiasis (sleeping sickness)
Yellow fever

Cerebral malaria is a syndrome characterized by diminished consciousness, seizures, or both. In endemic areas, it typically occurs in young children and manifests clinically as coma with or without convulsions. The Blantyre coma scale is frequently used to measure the level of consciousness in children.[520] Seizures may be clinically inapparent, subtle motor, partial motor, generalized tonic-clonic, or partial motor with secondary generalization.[521] Multiple factors can contribute to cerebral malaria: hypoglycemia, acidosis, hyperpyrexia, the postictal state, and effects of anticonvulsant medication. In endemic areas, there may also be considerable overlap in the clinical presentations of cerebral malaria and other syndromes, such as bacterial or viral meningitis, subdural hematoma, or sepsis.[133] Although cerebral malaria commonly resolves without neurologic sequelae,[522] some children (especially those with status epilepticus) may develop psychosis, cerebellar ataxia, extrapyramidal rigidity, hemiplegia, or long-term cognitive and language impairment.[523–527]

Respiratory distress is characterized by dyspnea or deep breathing (Kussmaul respirations), which may be accompanied by nasal flaring or intercostal retraction. In one study, deep breathing was 91% sensitive and 83% specific for the presence of severe metabolic acidosis (base excess ≤ −12), the underlying cause of respiratory distress.[59] *Prostration* from fluid and electrolyte depletion is determined by clinical judgment. If a child is 7 months of age or older, prostration may be defined as inability to sit unassisted. *Hyperparasitemia* is defined in endemic areas by WHO as parasite density of 500,000/μL or greater (approximately 10% parasitemia) and is associated with severe anemia, hypoglycemia, cerebral malaria, and renal failure. Although the severity of disease is generally thought to correlate with parasite density, nonimmune individuals may present with severe malaria at any parasitemia, even at levels that may be difficult to detect by microscopy. *Severe anemia* is defined in endemic areas as hemoglobin of 5 g/dL or less. Nonimmune individuals can present with signs and symptoms of severe anemia at hemoglobin levels significantly higher than 5 g/dL because of dehydration; with fluid repletion, rapid reductions from baseline hemoglobin levels can aggravate the symptoms of severe anemia. *Hypoglycemia* is defined as blood glucose of 40 mg/dL or less and may contribute to diminished consciousness and seizures.

Hyperbilirubinemia (manifesting as icterus or jaundice) is also an indicator of severe malaria and may reflect underlying liver compromise. *Renal insufficiency* of severe malaria is defined in endemic areas as anuria for at least 24 hours. However, an infected nonimmune patient with any evidence of renal insufficiency, even that caused by hypovolemia and improved with fluid replacement, should be considered to have severe malaria. *Hemoglobinuria* manifests as dark (cola) colored urine ("blackwater fever"), distinct from the red appearance of hematuria. *Shock* of malaria is clinically indistinguishable from that of sepsis caused by gram-negative bacteria. Special caution needs to be taken in the evaluation of shock because concurrent sepsis is frequently present with parasitemia in severe malaria. In addition to potentiating hypoglycemia, *cessation of eating and drinking* contributes to hypovolemia and consequently to severe acidosis and respiratory distress. *Repetitive vomiting* also contributes to hypovolemia and may complicate oral treatment of severe malaria in resource-poor countries, where parenteral therapy is not readily available. Medications used to treat malaria (e.g., mefloquine) may also cause vomiting, often warranting directly observed therapy. *Hyperpyrexia* is defined as axillary temperature of 40°C or greater and likely contributes to the severity of malaria through its association with febrile seizures.

DISTINGUISHING MALARIA FROM OTHER ILLNESSES WITH SIMILAR CLINICAL PRESENTATIONS

The differential diagnosis of the malaria presentation is broad and includes many febrile illnesses (Table 274.2). However, malaria should always lead the list in the differential diagnosis of fever in travelers or immigrants who have been in an endemic area within the previous 3 months and remain in consideration for years afterward. Travelers and immigrants often present with common ailments, and physicians must be alert to recognize and treat malaria to avoid a morbid or fatal outcome,[528–531] especially when they are working in temperate zones and do not often see malaria and other tropical diseases. It is estimated that 30 million travelers visit malaria-endemic regions each year. In 2003, cases of malaria acquired by international travelers were estimated to number 25,000 annually, of which 10,000 were reported and 150 were fatal.[532]

Clinical criteria to distinguish malaria from other illnesses are critical because RDTs for those illnesses are often limited or not available, and definitive diagnoses often require nonroutine methods of pathogen isolation or serologic testing that rely on comparisons of acute and convalescent antibody titers 2 to 4 weeks later. The probabilities of specific diseases are affected by geographic area visited (e.g., yellow fever is not prevalent in Asia or India), type of travel (e.g., adventure travelers to Lake Malawi are more likely to acquire schistosomiasis or leptospirosis from fresh water contact than are visitors to Nairobi, Kenya), time of travel (e.g., dengue fever is much less likely to be acquired during the dry season, when mosquito transmission is markedly reduced), type of food and water ingested (e.g., enteric fever is relatively unlikely in persons consuming only cooked food and bottled water), and vaccination history (e.g., the efficacy of yellow fever, hepatitis A, and hepatitis B vaccines makes these diseases unlikely if the patient is vaccinated). Self-reported compliance with mosquito repellents and malaria chemoprophylactic drugs, especially during the posttravel period, should *not* be used to rule out malaria because these reports are often inaccurate, and no preventive regimen is 100% effective. Features of selected infectious diseases that may occur as for malaria are briefly summarized in the following paragraphs.

Influenza

Like malaria, influenza may present with fever, headache, myalgias, and malaise. Prominent upper respiratory symptoms (rhinorrhea, sore throat, or dry cough) may help to distinguish influenza from malaria. The symptoms of many cases of malaria that were ultimately fatal to returned travelers in North America have been initially and mistakenly attributed to influenza.

Enteric Fever

Salmonella typhi and *Salmonella paratyphi* can be acquired in developing countries worldwide. As for malaria, patients with enteric fever may present with fever, headache, nausea, malaise, anorexia, and myalgias. Prominent gastrointestinal symptoms (abdominal pain, constipation, or diarrhea), the findings of rose spots or relative bradycardia, and a history of unsanitary food or water consumption may help to support

a diagnosis of enteric fever. A history of prior vaccination against *S. typhi* may not be useful in ruling out enteric fever because it is only 50% to 80% effective and does not protect against paratyphoidal illness.

Bacteremia/Sepsis

The fever, hypotension, evidence of poor peripheral perfusion, altered mental status, and multiorgan dysfunction that characterize bacteremia and sepsis can mimic severe malaria. One study found that bacteremia accompanied *P. falciparum* infection in 12% of young children who were admitted to a hospital with the primary diagnosis of severe malaria.[533]

Dengue Fever

Patients with classic nonhemorrhagic dengue fever may present with fever, headache, nausea, malaise, or anorexia. Myalgias tend to be much more severe than those experienced during malaria episodes. Dengue fever may be distinguished from malaria by its centrifugal rash, petechiae, lymphadenopathy, conjunctival injection, pharyngeal erythema, and relative bradycardia. Although dengue virus is also transmitted by mosquitoes during the rainy season in tropical regions worldwide, its incubation period of 4 to 7 days is not at all typical of malaria.

Acute Schistosomiasis (Katayama Fever)

Schistosoma trematodes are acquired from freshwater exposure (wading, swimming) in tropical regions worldwide. Patients with acute schistosomiasis may present 4 to 8 weeks after exposure with fever, headache, myalgias, malaise, and anorexia. Acute schistosomiasis can be distinguished from malaria by generalized urticaria and the findings of a pruritic rash at the site of cercarial penetration (usually on the legs), lymphadenopathy, and blood eosinophilia. Patients may present initially with focal neurologic signs as a result of egg dissemination to the central nervous system.

Leptospirosis

Leptospira interrogans spirochetes are acquired from freshwater or soil exposure in tropical and temperate regions worldwide. Patients with leptospirosis usually present within 7 to 12 days of exposure with fever, headache, nausea, and myalgias. Leptospirosis can be distinguished from malaria by the findings of conjunctival suffusion or rash but may progress to hepatic and renal insufficiency marked by hemorrhagic manifestations and pronounced hyperbilirubinemia (Weil syndrome). This complication is similar to a severe malaria presentation, but extremely high bilirubin levels are more characteristic of Weil syndrome.

African Tick Fever

Rickettsia africae is transmitted by tick bites, usually acquired during game hunting or safari travel to southern Africa between April and November. Presenting symptoms of African tick fever may be fever, headache, and myalgias and can be differentiated from malaria by the findings of lymphadenitis or multiple inoculation eschars.

East African Trypanosomiasis (Sleeping Sickness)

Trypanosoma brucei rhodesiense causes the acute form of African sleeping sickness and is acquired from tsetse fly bites, typically in association with game and brush in eastern and southern Africa. Trypanosomiasis may present with fever, headache, myalgias, malaise, and anorexia, yet it may be differentiated from malaria by a red chancre at the bite site, posterior cervical lymphadenopathy, or rash. Like malaria, it may progress to involve multiple organs, including the central nervous system.

Yellow Fever

Yellow fever virus is acquired from mosquito bites in tropical regions worldwide. It is characterized by fever, headache, myalgias, nausea, anorexia, and jaundice. Yellow fever may be differentiated from malaria by the presence of conjunctival suffusion or relative bradycardia and by its short incubation period (average, 3–6 days). Yellow fever is extremely unlikely in patients who have been vaccinated against it within the previous 10 years. As with severe malaria, patients may appear acutely ill and progress to liver failure and hemorrhagic manifestations, multiorgan system failure, and death.

THERAPY (see also Chapter 41)

General Principles

P. falciparum malaria can be fatal if not diagnosed and treated promptly and appropriately. This is especially true of nonimmune travelers returning from visits to malaria-endemic areas.[519,534,535] Malaria is a disease of protean manifestations.[536] Its diagnosis can be delayed by the nonspecificity of the clinical presentation and routine laboratory tests, especially if blood smears (and, if available, RDTs) are not promptly examined. Life-threatening manifestations of malaria, such as convulsions, hypoglycemia, and pulmonary edema, may develop rapidly in patients who appear relatively well at presentation or appear to respond initially to antimalarial drugs.[172]

Although some patients with uncomplicated *P. falciparum* malaria can be treated successfully in an outpatient setting,[537] patients with no immunity against the disease are at increased risk for sudden development of severe complications and should be hospitalized for at least 48 hours to ensure adequate response to therapy, regardless of how well they appear at presentation. Hospitalization is likewise recommended for individuals from malaria-endemic countries but whose immune status nevertheless cannot be known with certainty.[538] Acute *P. falciparum* malaria in a nonimmune individual can be dangerous and unpredictable; even without warning signs at presentation, a patient's condition may deteriorate dramatically after prompt hospitalization and apparently adequate treatment.[538] Contributing factors in such cases may include (1) replication of the parasites and their synchronous development into mature forms that sequester in the brain, leading to cerebral malaria, and (2) complications from the infection that lead to acute renal failure, lung injury, or hepatic insufficiency, even when the parasitemia is decreasing or the patient appears to be improving in other ways. Pregnant women, young children, and the elderly are at increased risk of morbidity and mortality and should be hospitalized regardless of their clinical state.[539–542]

Patients with *P. vivax, P. ovale,* or *P. malariae* malaria infrequently require hospitalization, although it is certainly necessary in cases with severe manifestations.[56,57] Patients with *P. knowlesi* malaria may require hospitalization because life-threatening manifestations of disease can develop rapidly.[18]

Uncomplicated Malaria

Treatment of uncomplicated *P. falciparum* malaria should always be initiated emergently because the risk of its morbidity and mortality increases with even short delays in medical care.[543] Uncomplicated malaria can be treated with oral medication if the patient is able to retain the drug; directly observed therapy may be appropriate in some cases to ensure adequate treatment. Drugs currently recommended for treating uncomplicated malaria are listed in Table 274.3. Most antimalarials, *except* for halofantrine (not available in the United States), doxycycline or tetracycline, and primaquine, can be safely used in pregnant or breastfeeding women.[544,545]

Because of widespread and ever-changing patterns of drug resistance in the world today, there is no blanket recommendation for antimalarial use, and treatment options must be carefully considered. Chloroquine can be used to treat uncomplicated *P. falciparum* malaria acquired from areas where chloroquine resistance has *not* been reported: Mexico, Central America west of the Panama Canal, Haiti, the Dominican Republic, and most areas of the Middle East. Chloroquine can also be used to treat uncomplicated malaria caused by any of the other four human malaria parasites, except for *P. vivax* malaria acquired in Papua New Guinea and Indonesia.

The blood-stage parasites of chloroquine-resistant *P. falciparum* or *P. vivax* uncomplicated malaria can be treated with the combination drugs atovaquone-proguanil[546] or artemether-lumefantrine,[547] both of which are highly effective in nonimmune individuals[548,549] (treatment to prevent relapse from *P. vivax* hypnozoites is discussed later). An alternative regimen is quinine plus doxycycline (or tetracycline or

TABLE 274.3 Malaria Treatment

DRUG	ADULT DOSE	PEDIATRIC DOSE[b]	PRECAUTIONS
Uncomplicated Malaria: Chloroquine-Resistant *Plasmodium falciparum*[c] or Chloroquine-Resistant *Plasmodium vivax*[d]			
***Atovaquone-Proguanil (Malarone)*[e]**			
Supplied in fixed-dose combination tablets containing 250 mg atovaquone and 100 mg proguanil (*adult* tablets) or 62.5 mg atovaquone and 25 mg proguanil (*pediatric* tablets)	Four adult tablets daily for 3 d (may be administered as 2 tablets 2× daily)	The number of *pediatric* or *adult* tablets taken daily for 3 d depends on patient's weight: 5–8 kg: 2 pediatric tablets 9–10 kg: 3 pediatric tablets 11–20 kg: 1 adult tablet 21–30 kg: 2 adult tablets 31–40 kg: 3 adult tablets >40 kg: 4 adult tablets	Not recommended in pregnant or breastfeeding women or infants weighing <5 kg. Take with food or whole milk. If patient vomits within 30 min of taking a dose, the dose should be repeated.
Artemether-Lumefantrine (Coartem)			
Supplied in fixed-dose combination tablets containing 20 mg artemether and 120 mg lumefantrine	Six-dose regimen: first day: 4 tablets initially, then 4 tablets 8 h later second day: 4 tablets 2× daily third day: 4 tablets 2× daily	Number of tablets per dose taken according to adult schedule depends on patient's weight: 5–14 kg: 1 tablet 15–24 kg: 2 tablets 25–34 kg: 3 tablets ≥35 kg: 4 tablets	Can be used in second and third trimesters of pregnancy and, if no other option is available, in first trimester of pregnancy. Not recommended in infants weighing <5 kg.[f] Take with food or whole milk. If patient vomits within 30 min of taking a dose, the dose should be repeated.
***Quinine Sulfate Plus One of the Following: Doxycycline, Tetracycline, or Clindamycin*[g]**			
Quinine sulfate supplied in 325-mg salt tablets. Doxycycline supplied in 100-mg tablets. Tetracycline supplied in 250-mg tablets. Clindamycin supplied in 300-mg capsules.	Quinine sulfate, 650 mg salt 3× daily for 3 d[h] *plus* either doxycycline, 100 mg 2× daily for 7 d, *or* tetracycline, 250 mg 4× daily for 7 d, *or* clindamycin, 20 mg/kg/d divided 3× daily for 7 d	Children ≥8 yr old: quinine sulfate, 10 mg salt/kg 3× daily for 3 days[h] *plus*[i] either doxycycline, 3 mg/kg daily for 7 d, *or* tetracycline, 25 mg/kg/d divided 4× daily for 7 d, *or* clindamycin, 20 mg/kg/d divided 3× daily for 7 d	Do not use doxycycline or tetracycline in children <8 yr old; use Malarone or Coartem for chloroquine-resistant *P. falciparum* or Malarone or mefloquine for chloroquine-resistant *P. vivax* instead. Do not use doxycycline or tetracycline in pregnant or breastfeeding women; use clindamycin instead.
***Mefloquine*[j] (Lariam, Generics)**			
Supplied in 250-mg salt tablets	750 mg salt, then 500 mg salt 6–12 h later	15 mg salt/kg, then 10 mg salt/kg 6–12 h later	Do not administer to individuals with cardiac conduction abnormalities, history of seizures, or serious psychiatric illnesses (e.g., psychosis, major depression). Do not use concomitantly with quinidine, quinine, or halofantrine.
Uncomplicated Malaria: Chloroquine-Sensitive *P. falciparum*; Chloroquine-Sensitive *P. vivax*,[k] *P. ovale*, *P. malariae*, or *P. knowlesi*			
Chloroquine Phosphate (Aralen, Generics)			
Supplied in 300-mg base tablets	600 mg base, then 300 mg base at 6, 24, and 48 h	10 mg base/kg (max. 600 mg base), then 5 mg base/kg at 6, 24, and 48 h	None. Safe in pregnant women.
Severe Malaria			
***Quinidine gluconate*[l]**			
Not available in the United States	Intravenous: 10 mg salt/kg loading dose (max. 600 mg) in normal saline infused slowly at a constant rate over 1–2 h, then continuous infusion of 0.02 mg salt/kg/min for at least 24 h until parasitemia <1% and patient can take oral therapy[m]	Intravenous: same dosing as for adults[m]	Do not administer as a bolus. Check blood glucose every 4–6 h during first 24 h of therapy. Administer 5%–10% dextrose along with quinidine to reduce risk of hypoglycemia. Monitor drug levels to keep between 3 and 8 μg/mL.
Artesunate			
Available in the United States from the CDC through an IND protocol	Intravenous: artesunate, 2.4 mg/kg, then 2.4 mg/kg at 12, 24, and 48 h[n]	Intravenous: for children >20 kg, same dosing as adults; children <20 kg use 3.0 mg/kg at 0, 12, 24, and 48 h[n]	None.
Quinine dihydrochloride			
Not available in the United States	Intravenous: 20 mg/kg loading dose in 5% dextrose infused slowly at a constant rate over 4 h, followed by maintenance dose 10 mg/kg over 3–4 h at 8-h intervals (max. 1800 mg/d) until oral therapy can be started[m]	Intravenous: same dosing as for adults[m]	Do not administer as a bolus. Check blood glucose every 4–6 h during first 24 h of therapy. Administer 5%–10% dextrose along with quinine to reduce risk of hypoglycemia.
Artemether			
Not available in the United States	Intramuscular: artemether, 3.2 mg/kg on first day, then 1.6 mg/kg daily for 4 d[n]	Intramuscular: same dosing as for adults[n]	None.

TABLE 274.3 Malaria Treatment—cont'd

DRUG	ADULT DOSE	PEDIATRIC DOSE[b]	PRECAUTIONS
Prevention (Terminal Prophylaxis) of Relapsing Malaria: *P. vivax* or *P. ovale*			
Primaquine Phosphate			
Supplied in 15-mg base tablets	30 mg base once daily for 14 d after departure from malaria-endemic area	0.5 mg base/kg once daily for 14 d (max. 30 mg base/d) after departure from malaria-endemic area	Test patient for G6PD deficiency and administer *only* if enzyme activity is normal.[o] Do *not* administer to pregnant or breastfeeding women.[p] Take with food.

[a]If a person develops malaria while taking a drug as prophylaxis, that drug should not be used as part of his or her treatment regimen. Use another option instead.
[b]Pediatric doses should *never* exceed the adult dose.
[c]Suspect chloroquine-resistant *P. falciparum* malaria in all areas *except* Mexico, Central America west of the Panama Canal, Haiti, the Dominican Republic, and most areas of the Middle East.
[d]Suspect chloroquine-resistant *P. vivax* malaria in Papua New Guinea and Indonesia.
[e]This regimen can also serve as presumptive self-treatment in travelers who have febrile illness but no immediate access to medical care. This regimen is not recommended for self-treatment of individuals on atovaquone-proguanil prophylaxis.
[f]Data from Ballard S-B, Salinger A, Arguin PM, et al. Updated CDC recommendations for using artemether-lumefantrine for the treatment of uncomplicated malaria in pregnant women in the United States. *MMWR.* 2018;67:424–431. https://www.cdc.gov/mmwr/volumes/67/wr/mm6714a4.htm?s_cid=mm6714a4_w.
[g]Because there are more data on the efficacy of quinine *plus* doxycycline or tetracycline, these combinations are preferred to quinine *plus* clindamycin.
[h]For infections acquired in Southeast Asia, where reduced susceptibility to quinine has been reported, treat with quinine sulfate for 7 days.
[i]Pediatric dosing may be difficult due to the unavailability of noncapsule forms of quinine.
[j]Mefloquine is recommended only if Malarone, Coartem, or quinine sulfate *plus* doxycycline (or tetracycline or clindamycin) cannot be used because of the higher rates of severe neuropsychiatric reactions at treatment doses. Mefloquine is *not* recommended for treatment of *P. falciparum* infections acquired in Southeast Asia because of drug resistance.
[k]If a patient does not respond to chloroquine, switch to a regimen for chloroquine-resistant *P. vivax* and notify the CDC via its Malaria Hotline.
[l]No longer available in the United States.
[m]Complete therapy with a quinine sulfate *plus* doxycycline (or tetracycline) regimen to complete a 7-day total course of therapy. In pregnant or breastfeeding women or children younger than 8 years, substitute clindamycin for doxycycline (or tetracycline).
[n]To prevent parasite recrudescence after artemisinin monotherapy, complete treatment with a standard course of atovaquone-proguanil, doxycycline (or tetracycline), clindamycin (in pregnant women), or mefloquine given orally.
[o]If G6PD activity is borderline, or as an alternative, administer primaquine, 45 mg base weekly for 8 consecutive weeks. If G6PD activity is deficient, contact the CDC or an infectious diseases/tropical medicine specialist for advice.
[p]Pregnant women requiring terminal prophylaxis should receive chloroquine 300 mg base weekly until delivery, and then primaquine after delivery if G6PD activity is normal and there is no breastfeeding.
CDC, Centers for Disease Control and Prevention; *G6PD,* glucose-6-phosphate dehydrogenase; *IND,* Investigational New Drug.
Drug regimens modified from CDC. Guidelines for Treatment of Malaria in the United States. *https://www.cdc.gov/malaria/resources/pdf/TreatmentTable_2018.pdf.*

clindamycin). Mefloquine is recommended only if atovaquone-proguanil, artemether-lumefantrine, or quinine plus doxycycline cannot be used because of the higher rates of severe neuropsychiatric reactions at treatment doses.[550] Because of drug resistance, however, mefloquine is *not* recommended for *P. falciparum* malaria acquired in Southeast Asia.

If a patient cannot tolerate oral therapy, parenteral formulations of antimalarial drugs must be administered (see later). Up-to-date information on malaria treatment and assistance with the management of suspected cases of malaria are available from the CDC Malaria Hotline (770-488-7788 or 855-856-4713 toll-free, Monday through Friday, 9:00 AM to 5:00 PM EST; 770-488-7100 after hours, weekends, and holidays). Current guidelines for malaria treatment in the United States are also available from the CDC (https://www.cdc.gov/malaria/resources/pdf/TreatmentTable_2018.pdf).

Chloroquine Phosphate

Chloroquine is considered safe in pregnant women (all trimesters)[551,552] and in children of all ages, including newborns. It has a bitter taste and may cause nausea or vomiting (take with food to ameliorate gastrointestinal symptoms), headache, dizziness, blurred vision, or dysphoria. Chloroquine commonly produces a nonallergic pruritus in dark-skinned persons and may exacerbate psoriasis. It is associated with retinal toxicity at high doses taken for chronic illnesses[553] but not at doses taken for malaria. Acute chloroquine toxicity can produce convulsions, hypotension and shock, and cardiorespiratory arrest.[554]

Atovaquone-Proguanil (Malarone)

Atovaquone-proguanil is used to treat uncomplicated malaria caused by multidrug-resistant *P. falciparum*[356,381,555] and is relatively well tolerated, although almost one-fourth of patients have gastrointestinal side effects.[556–558] Only rarely has atovaquone-proguanil been associated with severe adverse reactions.[559,560] Clearance of parasites is relatively slow: only 66% at 3 days.[556] Atovaquone-proguanil resistance is rare, being confined to case reports in mostly nonimmune individuals in whom recrudescence and initial treatment failure have been documented.[378–380,428,429,561–565]

Artemisinin-Based Combination Therapies

ACTs[566] are the first-line recommended treatments for uncomplicated *P. falciparum* malaria,[556,567] including in children and pregnant women during the second and third trimesters.[568] An ACT is a 3-day regimen of artemisinin or one of its derivatives (i.e., artesunate, artemether, or dihydroartemisinin) in combination with a partner drug (i.e., amodiaquine, mefloquine, lumefantrine, piperaquine, or pyronaridine). Although artemisinins are potent and fast acting, recrudescences are frequent after their use as monotherapy, and long-acting partner drugs are therefore needed to ensure cure.[569] Patterns of resistance to partner drugs determine which ACT should be used in particular geographic locations. Because of widespread resistance to chloroquine, ACTs that contain amodiaquine or lumefantrine are commonly used in Africa.[570] After a period of declining efficacy of mefloquine in Southeast Asia, ACTs containing piperaquine were increasingly used in this region.[571–579] Piperaquine, however, is now threatened by the rapid rise of resistance,[580,581] but with some return of mefloquine susceptibility; artesunate-mefloquine may therefore be useful in rotation against *P. falciparum* strains that are resistant to dihydroartemisinin-piperaquine.[582] Artesunate-pyronaridine has been shown to be an effective treatment in Western Cambodia, where multidrug-resistant *P. falciparum* is highly prevalent.[583,584]

A fixed-dose combination of artemether-lumefantrine (Coartem)[585] is the only ACT that is FDA-approved for use in the United States. For adults, four tablets are given initially and repeated at 8, 24, 36, 48, and 60 hours.[556] This ACT should be taken if possible with a high-fat snack to maximize absorption of lumefantrine. Combinations of dihydroartemisinin-piperaquine (Eurartesim)[586] and artesunate-pyronaridine (Pyramax)[587] are licensed for use in Europe.

Quinine Plus Doxycycline

The combination of quinine plus doxycycline is effective against multidrug-resistant parasites. To prevent parasite recrudescence after quinine monotherapy, doxycycline (or tetracycline or clindamycin) is given as a partner drug. Quinine has a bitter taste and may cause gastrointestinal upset and cinchonism[588] (nausea, vomiting, dysphoria,

tinnitus, and high-tone deafness). Hypoglycemia from quinine-induced insulin secretion can be an adverse event, particularly in pregnancy.[554] Quinine is considered safe in pregnant women (all trimesters).[552] Doxycycline also causes gastrointestinal upset and commonly results in vaginal candidiasis, requiring concomitant use of antifungal suppositories. The requirement for multiple doses over 7 days and the gastrointestinal upset caused by both drugs may reduce the compliance and hence effectiveness of this regimen.[589] The use of all tetracyclines is contraindicated in children younger than 8 years or in pregnant women because of adverse effects on tooth and bone development. In these cases, clindamycin may be a safe and effective substitute for doxycycline.[590–593]

Mefloquine

Mefloquine can be used to treat most chloroquine-resistant parasites except for strains in areas such as Cambodia, Thailand, Myanmar, and Vietnam, where resistance against this drug is present.[557] It may cause gastrointestinal upset, vomiting, dysphoria, dreams, mood changes, and neuropsychiatric reactions in a significant proportion of patients,[594–596] although there is no evidence for increased first-time diagnosis of depression with mefloquine relative to other commonly used antimalarials.[597] Mefloquine is cleared slowly because its elimination half-life is 2 to 3 weeks. Because mefloquine may prolong the corrected QT (QTc) interval, it cannot be administered concurrently with quinine or quinine-like drugs (e.g., quinidine, halofantrine). Mefloquine should not be used in persons with cardiac conduction diseases because it can aggravate conduction abnormalities.

Standby Emergency Treatment of Uncomplicated Malaria in Travelers

Because treatment delay increases morbidity and mortality associated with malaria, travelers to isolated areas may benefit from standby emergency treatment while they actively seek medical care.[598] Standby antimalarials may be advised to travelers for emergency self-treatment of fever or other symptoms compatible with malaria that occur at least 1 week after entering an endemic area. Drugs used for this purpose include atovaquone-proguanil, artemether-lumefantrine, artesunate-pyronaridine (available in Europe), and dihydroartemisinin-piperaquine (available in Europe), all of which are likely to be effective in all malaria-endemic areas because of lack of significant drug resistance. Although standby emergency treatment can be safe, effective, and potentially lifesaving, no regimen is currently registered for this use in any country. No randomized controlled clinical trials have been or are likely to be performed because of the high morbidity and mortality of untreated or inappropriately treated malaria in nonimmune individuals. Travelers should be discouraged from self-treatment with the same drug they are using for chemoprophylaxis or with locally acquired products that may be of poor quality or outright fake.[599–604]

Intermittent Presumptive Treatment in Infants, Children, and Pregnant Women

In areas with intense transmission, infants 6 to 12 months of age suffer multiple episodes of malaria and are therefore at risk for life-threatening severe anemia.[158,605] Weekly chemoprophylaxis of infants protects against malarial fevers as well as anemia but may compromise development of natural immunity.[606,607] Intermittent presumptive treatment (IPT, e.g., amodiaquine every 2 months for a total of 6 months; also known as intermittent preventative treatment) of infants can reduce malaria morbidity by 50% to 65% during the first year of life while still allowing sufficient exposure to parasites and development of immunity.[608,609] In areas with seasonal malaria transmission, IPT in children younger than 5 or 6 years reduces the incidence of uncomplicated and severe malaria.[158,610] In areas of endemic transmission, malaria of pregnancy is associated with severe maternal anemia and low birth weight in newborns. IPT has been shown to reduce the risk of severe anemia in women who received one to three doses of SP over the duration of their first pregnancy.[611] A systematic review and meta-analysis of seven trials in sub-Saharan Africa showed that IPT with three or more doses of SP was associated with a lower risk of low birth weight than two-dose regimens.[612] A meta-analysis of 32 national cross-sectional data sets in Africa showed that preventing malaria with IPT and insecticide-treated nets in pregnant women substantially reduces neonatal mortality and low birth weight.[613] These and other studies support the WHO recommendation to provide at least three doses of IPT during pregnancy at each antenatal visit.

Seasonal Malaria Chemoprevention

Seasonal malaria chemoprevention (SMC) is defined as the intermittent administration of full treatment courses of antimalarial drugs to children in areas with highly seasonal transmission during the malaria season. SMC aims to reduce the incidence of falciparum malaria in areas where the youngest children are most vulnerable to severe disease and death, and where *P. falciparum* remains largely susceptible to appropriate regimens. For example, WHO recommends[614] monthly doses of amodiaquine *plus* SP in children ages 6 months to 5 years in areas with highly seasonal malaria transmission (typically for 3–4 months) in the Sahelian region of Africa. This intervention, which is safe and cost-effective and can be administered by community health workers, has been shown to be 75% protective against uncomplicated and severe malaria in this setting.

Mass Drug Administration

In contrast to SMC, which treats a subpopulation of young children but does not address the reservoir of transmittable parasites from older children and adults, mass drug administration (MDA) aims to clear parasites from all individuals. MDA is of particular interest for its use in control programs that aim to dramatically reduce and eventually eliminate malaria.[615] Island regions with monitored migration have used MDA to move toward elimination; sustainable successes in these settings recognize the critical role of high-level community engagement and unwavering commitments to permanent surveillance and outbreak control.[616,617]

Severe Malaria

Successful treatment of patients with severe malaria requires frequent clinical monitoring and intensive nursing care and may demand sophisticated interventions, such as continuous electrocardiography (ECG), hemodynamic monitoring, mechanical ventilation, or hemodialysis. Replacement of blood and fluids can lead to rapid reductions in lactate, resolution of metabolic acidosis, improvement in renal function, and clinical improvement of critically ill children.[618] On the other hand, liberal fluid resuscitation in adults may *not* improve acid-base status or renal function and may promote the development of pulmonary edema.[619]

Quinidine gluconate is the only FDA-approved parenteral treatment for severe malaria in the United States, but the intravenous formulation is no longer available in the United States as of this writing.[620,621] Intravenous artesunate is now the preferred treatment for severe malaria in the United States. Artesunate is much safer than intravenous quinidine and is readily available from the CDC through its Malaria Hotline (see hours and phone numbers under "Uncomplicated Malaria" earlier).[620]

Outside the United States, parenteral formulations of artemisinin derivatives and quinine are widely used to treat severe malaria, and rectal suppositories of artesunate are available for the emergent treatment of severe malaria if patients cannot be treated orally and access to injections will take several hours.[534,623] In Canada, intravenous formulations of artesunate and quinine are available through the Canadian Malaria Network (https://www.canada.ca/en/public-health/services/travel-health/medical-access-artesunate-quinine-malaria-treatment.html). Antimalarial drug regimens used to treat severe malaria are presented in Table 274.3.

Quinidine Gluconate

Many physicians will be unfamiliar with quinidine because this drug has been replaced by newer antiarrhythmic agents. Quinidine has a narrow therapeutic window and must be used with extreme care in an intensive care unit.[620] Its use in consultation with a cardiologist or a physician with experience in treating malaria is advised. It is administered intravenously as an infusion until the patient improves clinically and can complete antimalarial treatment orally. Quinidine levels should be monitored throughout the period of its administration (see Table 274.3).

Quinidine is *never* administered as a bolus injection, which can cause fatal hypotension. Potentially fatal adverse reactions can occur even at treatment doses. It can cause postural hypotension, so frequent blood pressure measurements should be made. Quinidine may prolong the QTc interval, putting the patient at risk for ventricular tachycardias (e.g., torsades de pointes), and therefore should be administered with continuous ECG monitoring.[624] If QTc prolongation greater than 25% of baseline or hypotension unresponsive to fluid challenge develops, the infusion rate should be reduced or the infusion stopped. Because quinidine may cause hyperinsulinemic hypoglycemia, serum glucose must be monitored every 4 to 6 hours and with any acute neurologic change (e.g., diminished consciousness, convulsions) that may arise from severe hypoglycemia. Administration of 5% or 10% dextrose while infusing quinidine can reduce the incidence of hypoglycemia.

In patients taking medications that also prolong the QT interval, particularly when coadministered with drugs that suppress hepatic metabolism, the use of quinidine can be problematic. Although the initial loading dose of quinidine is not reduced in renal insufficiency, patients with malaria and acute renal failure may not clear quinidine effectively. Case reports illustrating the use of quinidine in the treatment of severe malaria have highlighted common clinical scenarios, such as adjustment of infusion rates associated with elevated quinidine blood levels; prolonged QTc intervals; and arrhythmias as well as hypoglycemia, hypotension, and vomiting.[624] Quinidine levels should be maintained below 8 µg/mL; this may require 30% to 50% dose reductions to prevent drug accumulation in patients who remain seriously ill after 3 days of treatment. The response to quinidine is assessed by frequent blood smears every 6 to 8 hours to ensure rapid decrease in parasitemia. Once the patient improves and can take oral medications without vomiting, quinidine can be discontinued, and a 7-day total course of treatment completed with a combination of quinine tablets and doxycycline.

Artemisinin and Its Derivatives

Artemisinin is derived from *Artemisia annua* (qing hao), an herbal plant used in China for 2000 years as therapy for fevers.[625] Artemisinin and its derivatives (artesunate, artemether, and dihydroartemisinin) are highly effective against multidrug-resistant parasites and result in rapid clearance of parasitemia and clinical improvement, usually within 24 to 36 hours. They are well tolerated and safe in adults, children, and pregnant women.[626,627] Millions of people have taken artemisinins with no significant adverse or treatment-limiting effects being reported.[628] Two large, multicenter, randomized trials conducted in Southeast Asian adults[629] and sub-Saharan African children[630] concluded that parenteral treatment with artesunate reduced mortality from severe falciparum malaria 22% to 35% more than did treatment with parenteral quinine. A review of eight randomized controlled trials found that parenteral or rectal artesunate was superior to parenteral quinine for treating severe malaria in both adults and children in different regions of the world.[631] Post-artesunate hemolysis occurs in 10% to 15% of patients receiving intravenous artesunate, particularly those with high parasite counts, usually beginning after the seventh day from the start of therapy. A mechanism that removes pitted, previously infected erythrocytes is thought to contribute to this phenomenon.[632–634] Patients should be informed of this and have their hemoglobin level checked around day 14.[556,635] The course is self-limited but may require red blood cell transfusion.

In June 2007, the Walter Reed Army Institute for Research and the CDC received FDA approval for a collaborative IND protocol for intravenous artesunate to treat severe malaria (https://www.cdc.gov/malaria/diagnosis_treatment/artesunate.html). Artesunate is provided by the CDC to hospitalized malaria patients on an emergency basis to treat those who need intravenous treatment for severe disease, who have high parasitemia, or who are unable to take oral medications.

Quinine Dihydrochloride

In some endemic areas, quinine is the only readily available drug for the parenteral treatment of patients who have severe malaria or patients with uncomplicated malaria who cannot take oral medication for reasons including vomiting. Quinine commonly causes hypoglycemia and the unpleasant side effects of cinchonism. Administration of quinine in a dextrose infusion and frequent (every 4–6 hours) glucose checks help to avoid hypoglycemia, which in some cases is life threatening. Quinine is much less cardiotoxic than quinidine, requiring no continuous ECG monitoring during its administration. Intravenous formulations of quinine are not commercially available in the United States, nor can they be obtained from the CDC on an emergency basis.

Bacteremia and Sepsis in Severe Malaria

In patients who present with a clinical picture consistent with sepsis syndrome, broad-spectrum antibiotics should be administered while awaiting blood culture results. Bacteremia complicating severe malaria is not uncommon in infants and children and may cause any patient's clinical status to deteriorate abruptly.[533,636,637]

Exchange Transfusion in Severe Malaria

High parasitemia has been correlated with mortality in falciparum malaria, leading to the use of exchange transfusion (ET) as an adjunct therapeutic measure.[638] ET may reduce parasite load, remove toxic substances, reduce microcirculatory sludging, and rapidly correct anemia. Although case reports and series claim beneficial effects of ET (including partial ET in young children),[639–644] a meta-analysis concluded that a randomized controlled trial is necessary to determine whether ET is beneficial.[645] ET may be harmful and is associated with fluid overload, risk of transfusion reactions and related infections, and line sepsis. In addition, ET does not remove infected erythrocytes that are sequestered in deep tissue capillary beds, including those in the brain. Exchange transfusion is no longer recommended by the CDC.

Nonfalciparum Malaria

All cases of malaria should be treated as falciparum malaria until proved otherwise because *P. falciparum* infections can rapidly become life threatening. Uncomplicated malaria caused by *P. vivax, P. ovale, P. malariae,* or *P. knowlesi* is treated with chloroquine, unless (1) it is acquired in geographic regions where these species are known or suspected to be chloroquine resistant (e.g., *P. vivax* in Papua New Guinea and Indonesia) or (2) any doubt exists as to the parasite species or if there is a mixed infection. Mixed infections consisting of two or more *Plasmodium* species may sometimes mask a chloroquine-resistant *P. falciparum* subpopulation that can emerge during or after treatment. The blood stages of *P. vivax* infections that are likely to be chloroquine resistant can be treated with quinine plus doxycycline, atovaquone-proguanil,[646] or mefloquine at doses listed in Table 274.3. The CDC does not currently recommend artemether-lumefantrine for treatment of nonfalciparum malaria, although significant clinical data support its use for this indication.[547,647,648] Infections with *P. knowlesi* can be treated with chloroquine unless severe manifestations are present,[649] in which case parenteral treatment with quinidine, an artemisinin derivative, or quinine would be indicated.

Persistent liver stages (hypnozoites) of *P. vivax* and *P. ovale* may be treated with primaquine (see Table 274.3) if there is no contraindication, but this treatment frequently fails because of noncompliance with the recommended 14-day regimen. After blood-stage *P. vivax* and *P. ovale* infections are treated with chloroquine (a drug *not* effective against hypnozoites), primaquine must be administered to prevent relapse.[650–652] Even when taken appropriately, however, this treatment may not always be successful because of interindividual variations of drug metabolism or variable parasite responses to low versus high drug doses.[653,654] Dihydroartemisinin-piperaquine *plus* primaquine has also been shown to be effective in treating and preventing relapses of chloroquine-resistant *P. vivax* malaria in Indonesia.[655] Taking primaquine with food ameliorates gastrointestinal side effects and improves compliance. Patients should be advised to discontinue this drug and seek medical evaluation if their urine becomes dark because primaquine occasionally can cause some hemolysis in persons with mildly deficient or even normal G6PD activity. Primaquine causes methemoglobinemia in nearly all persons treated, but this is rarely clinically significant (bluish discoloration of mucous membranes may be observed).

Primaquine is contraindicated in persons with severe forms of G6PD deficiency (e.g., Mediterranean type) or methemoglobin reductase deficiency because of the danger of massive and potentially fatal

hemolysis.[210] Persons with less severe forms of G6PD deficiency have been treated with standard primaquine doses, but significant decreases in hematocrit levels were observed in some cases.[656] In such individuals, weekly dosing of primaquine for longer periods (e.g., 8 weeks) has been recommended.[651,657] Primaquine should not be administered to pregnant women because of the risk of hemolytic disease in the fetus. Individuals who do not receive primaquine (including pregnant women) should be monitored for relapses, and if these occur, should be treated with blood-stage antimalarials. Primaquine should be administered to individuals who reside permanently in areas endemic for *P. vivax* or *P. ovale,* even if reinfection is likely. Primaquine is not administered to persons who acquire infection by transfusion or transplantation because hypnozoites develop only from mosquito-inoculated sporozoites. Tafenoquine[658] has been developed as a potential replacement for primaquine and continues to be evaluated for safety and efficacy in clinical trials (see Chapter 41).[659] Based on data from the recent GATHER and DETECTIVE[660] studies, the FDA in July 2018 approved single-dose tafenoquine 300 mg to prevent relapse of *P. vivax* malaria in patients aged 16 years and older. Pregnancy and G6PD deficiency are contraindications for tafenoquine use.

PREVENTION

Risk Assessment

The risk of acquiring malaria varies according to the geographic region visited,[661] travel destination within geographic areas (e.g., urban versus rural setting), type of accommodations (e.g., camping tent vs. air-conditioned hotel), duration of stay (e.g., a less than 1-week business trip vs. a 3-month travel adventure), time of travel (high- vs. low-transmission season), altitude of destination (<2000 meters vs. higher), and efficacy of and compliance with malaria prophylaxis measures.[662–664] First- and second-generation immigrants and their children living in nonendemic countries who return home to visit friends and relatives (so-called VFR travelers)[665,666] are at high risk for acquiring malaria[317] because they often do not take prophylaxis (thinking that malaria is not a serious threat because of their previous experience with it), are unaware they have "lost" immunity to malaria and are now at risk for severe disease, do not realize the risks of traveling when pregnant or when taking young nonimmune children to malarious regions, or are medically underserved and therefore less likely to seek pretravel advice.[667]

Chemoprophylaxis

Lack of proper chemoprophylaxis continues to be associated with severe complications from malaria and death.[317,543] Malaria is effectively prevented in travelers and in pregnant women in endemic areas by using antimalarial drugs when prescribed and taken appropriately (Table 274.4). In 2015, only 36 of 766 (4.7%) US residents who acquired malaria in an endemic area reported they had been compliant with a chemoprophylaxis regimen recommended by the CDC for their regions of travel.[317]

Selection of an effective prophylactic regimen depends on geographic patterns of drug resistance, medical conditions, concomitant medications, and other factors that may affect compliance: number of pills, dosing interval (i.e., daily vs. weekly), duration of travel, duration of pretravel and posttravel medication, cost, and the reputation as well as the actual tolerability of side effects.[663,668,669] Chemoprophylaxis recommendations change frequently because of regional and temporal variability in malaria risk, even within countries; the ongoing spread and independent emergence of drug-resistant parasites; and resurgence of malaria in areas previously free of the disease. Updates on outbreaks are reported by the CDC at https://www.cdc.gov/parasites/malaria/index.html. In 2012, for example, the CDC reported a series of updates on locally transmitted *P. vivax* malaria cases in Greece but did not recommend chemoprophylaxis for travelers to this country. Information on the geographic risk of acquiring malaria can be found by using the CDC's Infectious Diseases Related to Travel website (https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/malaria#5210).

Areas With Chloroquine-Sensitive Malaria

Currently, chloroquine (or hydroxychloroquine) can be used in travelers to those limited areas where chloroquine-resistant *P. falciparum* has *not* been reported, such as some areas of Central America and the Caribbean. Chloroquine is very well tolerated but may cause gastrointestinal disturbance, headache, dizziness, and pruritis, and may exacerbate psoriasis. Chloroquine may also cause retinopathy and arrhythmias when it accumulates because of excessive or prolonged dosing. Periodic funduscopic examination is therefore recommended with long-term use. Chloroquine prophylaxis has been used extensively and safely in pregnant and breastfeeding women[670,671] and in children of all ages, including newborns. Travelers who are exposed to *P. vivax* or *P. ovale* and have normal G6PD activity can receive terminal prophylaxis with primaquine on their return, as discussed earlier.

Areas With Mefloquine-Sensitive Malaria

Mefloquine can be used in travelers to areas where chloroquine-resistant *P. falciparum* has been reported,[672,673] *except* in areas where mefloquine resistance has also been reported: Thailand, Myanmar, southern China, Cambodia, Laos, and Vietnam. Mefloquine may prolong the QTc interval and so cannot be given to individuals with cardiac conduction abnormalities and should also not be administered concurrently with quinine or quinine-like drugs (e.g., quinidine, halofantrine), which can lead to sudden cardiac death. Mefloquine is also contraindicated in individuals with serious neuropsychiatric disorders (e.g., psychosis, major depression, or history of seizures). An estimated 5% of individuals report neuropsychological events, such as sleep disturbances, insomnia, nightmares, cognitive changes, anxiety, or depression, that led to drug discontinuation.[674,675] A systematic review of chemoprophylaxis studies identified eight randomized controlled trials meeting inclusion criteria and found that mefloquine use was associated with more reports of adverse neuropsychiatric events than with doxycycline or atovaquone-proguanil use.[550] In 2013, the FDA updated its label for mefloquine, warning that this drug may cause dizziness, balance problems, and ringing in the ears, which can occur at any time during use and can last for months to years after the drug is stopped or can become permanent. Although not approved for use during pregnancy (FDA pregnancy category B), mefloquine prophylaxis has been reported safe and effective during the second and third trimesters[676–678] and possibly during the first trimester.[679] Because most adverse effects are noted within the first three doses, starting prophylaxis 3 weeks before travel enables individuals to test their tolerance of the drug before they depart.

All Areas

Atovaquone-proguanil or doxycycline can be used in travelers to all areas, including where mefloquine-resistant *P. falciparum* has been reported, or in those travelers who are at risk of acquiring chloroquine-resistant malaria but who cannot take mefloquine.[672,680–683] Atovaquone-proguanil is safe, effective, and well tolerated in both short-term and long-term nonimmune travelers, and there are no contraindications to its use.[673,681,682,684–690] However, it is not recommended for children weighing less than 5 kg, individuals with severe renal impairment, or pregnant women. Although its safety profile in pregnancy has not been established, one study suggests that atovaquone-proguanil use in early pregnancy is not associated with the risk of major birth defects.[691] Atovaquone-proguanil failures have been reported from infections with *P. falciparum* strains that carry mutations in cytochrome *b*.[692]

Doxycycline frequently causes gastrointestinal upset (take with food) and may cause esophageal irritation and ulceration (take with water, sit up for 30 minutes), photosensitivity (use sunscreen), vaginal candidiasis (carry over-the-counter antifungal suppositories), and decreased effectiveness of hormonal contraceptive agents (use backup method). Doxycycline should not be used by pregnant or breastfeeding women and children less than 8 years of age because of deleterious effects on bone and tooth development. In addition, doxycycline should not be taken with metal-containing antacids, which can decrease its absorption. Actual effectiveness of doxycycline may be slightly lower than that reported from some studies because of frequent noncompliance with its daily dosing requirement.[693] Failure of properly taken doxycycline prophylaxis is unlikely because *Plasmodium* resistance has not been reported against this drug.

TABLE 274.4 Malaria Chemoprophylaxis

DRUG	ADULT DOSE	PEDIATRIC DOSE	PRECAUTIONS
Areas With Chloroquine-Sensitive Malaria ***Chloroquine Phosphate (Aralen, Generics)***			
Supplied in 300-mg base tablets	300 mg base once weekly[b]	5 mg/kg base once weekly, up to the maximum adult dose of 300 mg base[b]	Drug accumulation from prolonged use or inadvertent daily dosing may cause retinopathy. May exacerbate psoriasis.
Areas With Mefloquine-Sensitive Malaria ***Mefloquine (Lariam, Generics)***			
Supplied in 250-mg salt tablets	250 mg salt once weekly[c]	Dosed according to body weight: ≤9 kg: 5 mg/kg salt once weekly 10–19 kg: ¼ tablet once weekly 20–30 kg: ½ tablet once weekly 31–45 kg: ¾ tablet once weekly >45 kg: 1 tablet once weekly[c]	Do not use in individuals with cardiac conduction abnormalities, history of seizures, or serious psychiatric illnesses (e.g., psychosis, major depression). Do not use concomitantly with quinidine, quinine, or halofantrine. Do not use in first trimester of pregnancy.
All Areas ***Atovaquone-Proguanil (Malarone)***			
Supplied in fixed-dose combination tablets containing 250 mg atovaquone and 100 mg proguanil (adult tablet) or 62.5 mg atovaquone and 25 mg proguanil (pediatric tablet)	1 adult tablet daily[d]	Dose per body weight: 5–8 kg: ½ pediatric tablet daily 9–10 kg: ¾ pediatric tablet daily 11–20 kg: 1 pediatric tablet daily 21–30 kg: 2 pediatric tablets daily 31–40 kg: 3 pediatric tablets daily >40 kg: 1 adult tablet daily[d]	Take with food or whole milk. Not recommended for children weighing <5 kg, pregnant women, or women who breastfeed a child weighing <5 kg. Prophylactic dosing in children <11 kg constitutes off-label use in the United States. Contraindicated in individuals with severe renal impairment.
Doxycycline			
Supplied in 100-mg tablets	100 mg daily[e]	Children ≥8 yr old: 2.2 mg/kg up to adult dose of 100 mg daily[e]	Do not use in children <8 yr old or in pregnant women. May increase risk of sun sensitivity and vaginal yeast infection.
Areas With Mostly *P. vivax* ***Primaquine Phosphate***			
Supplied in 15-mg base tablets	30 mg base daily[f]	0.5 mg/kg base up to adult dose of 30 mg base daily[f]	Recommended for short-duration travel only. Contraindicated in individuals with G6PD deficiency and pregnant women. Also contraindicated in women who breastfeed, unless the infant being breastfed has a normal G6PD activity level.

[a]When several different drugs are recommended for an area, this table might help in the decision-making process (see https://www.cdc.gov/malaria/travelers/drugs.html).
[b]Beginning 1–2 weeks before travel and continuing *weekly* for 4 weeks after leaving a malarious area.
[c]Beginning 2–3 weeks before travel and continuing *weekly* for 4 weeks after leaving a malarious area.
[d]Beginning 1–2 days before travel and continuing *daily* for 7 days after leaving a malarious area.
[e]Beginning 1–2 days before travel and continuing *daily* for 4 weeks after leaving a malarious area.
[f]Beginning 1–2 days before travel and continuing *daily* for 7 days after leaving a malarious area.
G6PD, Glucose-6-phospate dehydrogenase.
Drug regimens modified from CDC. Drugs Used in the Prophylaxis of Malaria. *https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/malaria.*

Most antimalarial drugs (chloroquine, mefloquine, and doxycycline) are taken for 4 weeks after a person leaves a malarious area. This is to ensure that all liver-stage *P. falciparum* parasites, against which these drugs have no or questionable activity, have entirely completed their development into merozoites and passed into the bloodstream, where they can be killed by these drugs. Atovaquone-proguanil eradicates the liver stages of *P. falciparum,* although not those of *P. vivax.* The current recommendation is to take this drug for only 7 days after leaving a malarious area.

In some areas, multiple species of *Plasmodium* are transmitted to travelers by mosquitoes and can include *P. falciparum, P. vivax, P. ovale, P. malariae,* and even *P. knowlesi*[481,694,695] in various combinations of risk. Although the presence of chloroquine- or mefloquine-resistant *P. falciparum* might be used as the primary reason for selecting mefloquine, atovaquone-proguanil, or doxycycline prophylaxis against malaria, these drugs are also effective in preventing *P. vivax* malaria.[335,696] However, these drugs will not kill *P. vivax* (or *P. ovale*) hypnozoites in the liver to prevent malaria relapse,[697–699] so terminal prophylaxis with primaquine is necessary. For this reason, primaquine and tafenoquine[700] have been evaluated for primary prophylaxis of *P. falciparum* and *P. vivax* malaria in travelers to areas with primarily *P. vivax* who are not pregnant and have normal G6PD activity levels.[697,701,702] Based in part on a recent analysis of five clinical trials,[703] the FDA in August 2018 approved weekly dosing of tafenoquine for this indication in adult travelers.

Mosquito Repellent and Avoidance Measures

No chemoprophylactic regimen is 100% effective. Despite adequate serum mefloquine levels and other laboratory evidence of compliance, mefloquine prophylaxis has failed where mefloquine resistance is not thought to be common.[704] This example, as well as others, highlights the recommendation that measures to reduce mosquito bites should always accompany chemoprophylaxis.[705,706] Travelers can reduce mosquito bites by using *N, N*-diethyl-meta-toluamide (DEET)–containing insect repellents on exposed skin (applied after sunscreen),[707–709] wearing permethrin-treated clothing, wearing clothes and footwear that cover as much skin as possible,[704] sleeping under permethrin-treated bed nets,[710] staying in housing with air-conditioning and well-screened areas cleared of mosquitoes, and refraining from outdoor activity during peak *Anopheles* biting hours (from dusk to dawn).[711] For information on ordering insecticide-treated bed nets, see www.travmed.com.

Vaccination

Volunteers immunized under chloroquine prophylaxis with live *P. falciparum* sporozoites have been shown to develop long-lasting pre-erythrocytic immunity.[712] RTS,S, a vaccine based on a protein component (circumsporozoite protein) from the surface of *P. falciparum* sporozoites, proved safe, well tolerated, and immunogenic in initial clinical trials.[713] During an initial 12-month follow-up period in efficacy trials, the RTS,S vaccine conferred approximately 50% and 30% protection against *P.*

falciparum malaria in African children ages 5 to 17 months[714] and 6 to 12 weeks,[715] respectively. Over a 4-year follow-up period, however, the efficacy of the RTS,S vaccine declined from 44% to −0.4% in African children ages 5 to 17 months.[716] In July 2015, European regulators found the risk-benefit profile of RTS,S/AS01 (Mosquirix) to be favorable from a regulatory perspective for use as the world's first malaria vaccine.[717] Some recent publications review important concepts in malaria vaccinology and discuss the state of research in the field.[718–721] Progress has been made with vaccine candidates such as the Duffy-binding protein of *P. vivax*,[722,723] a PfEMP-1 molecule involved in *P. falciparum* malaria of pregnancy,[724] live or radiation-attenuated *P. falciparum* sporozoites,[725,726] and molecules critical to the invasion of erythrocytes by *P. falciparum* merozoites.[727]

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The complete reference list is available online at Expert Consult.

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