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Diagnosis, Treatment, and Prevention of Malaria in the US
A Review

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IMPORTANCE Malaria is caused by protozoa parasites of the genus *Plasmodium* and is diagnosed in approximately 2000 people in the US each year who have returned from visiting regions with endemic malaria. The mortality rate from malaria is approximately 0.3% in the US and 0.26% worldwide.

OBSERVATIONS In the US, most malaria is diagnosed in people who traveled to an endemic region. More than 80% of people diagnosed with malaria in the US acquired the infection in Africa. Of the approximately 2000 people diagnosed with malaria in the US in 2017, an estimated 82.4% were adults and about 78.6% were Black or African American. Among US residents diagnosed with malaria, 71.7% had not taken malaria chemoprophylaxis during travel. In 2017 in the US, *P falciparum* was the species diagnosed in approximately 79% of patients, whereas *P vivax* was diagnosed in an estimated 11.2% of patients. In 2017 in the US, severe malaria, defined as vital organ involvement including shock, pulmonary edema, significant bleeding, seizures, impaired consciousness, and laboratory abnormalities such as kidney impairment, acidosis, anemia, or high parasitemia, occurred in approximately 14% of patients, and an estimated 0.3% of those receiving a diagnosis of malaria in the US died. *P falciparum* has developed resistance to chloroquine in most regions of the world, including Africa. First-line therapy for *P falciparum* malaria in the US is combination therapy that includes artemisinin. If *P falciparum* was acquired in a known chloroquine-sensitive region such as Haiti, chloroquine remains an alternative option. When artemisinin-based combination therapies are not available, atovaquone-proguanil or quinine plus clindamycin is used for chloroquine-resistant malaria. *P vivax, P ovale, P malariae,* and *P knowlesi* are typically chloroquine sensitive, and treatment with either artemisinin-based combination therapy or chloroquine for regions with chloroquine-susceptible infections for uncomplicated malaria is recommended. For severe malaria, intravenous artesunate is first-line therapy. Treatment of mild malaria due to a chloroquine-resistant parasite consists of a combination therapy that includes artemisinin or chloroquine for chloroquine-sensitive malaria. *P vivax* and *P ovale* require additional therapy with an 8-aminoquinoline to eradicate the liver stage. Several options exist for chemoprophylaxis and selection should be based on patient characteristics and preferences.

CONCLUSIONS AND RELEVANCE Approximately 2000 cases of malaria are diagnosed each year in the US, most commonly in travelers returning from visiting endemic areas. Prevention and treatment of malaria depend on the species and the drug sensitivity of parasites from the region of acquisition. Intravenous artesunate is first-line therapy for severe malaria.

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Multimedia

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In 2020, approximately 241 million cases of malaria occurred in 85 countries with endemic malaria. Travelers to these regions are at risk for infection.[1] The number of people with malaria who arrive in the US has increased each year since 1972, from approximately 614 cases in 1972 to an 2161 cases in 2017.[2] Patients with malaria typically present to frontline US health care workers, who need to diagnose and manage this infection. This Review summarizes current evidence regarding the prevention, diagnosis, and treatment of malaria.

Methods

We searched the PubMed and Cochrane Library databases for English-language randomized clinical trials, meta-analyses, systematic reviews, and observational studies of the epidemiology, diagnosis, and treatment of malaria, published from January 2016 to March 2022. References were searched manually for additional relevant publications, including World Health Organization

publications. Randomized clinical trials and systematic reviews relevant to the generalist clinician were prioritized. Of 3964 articles identified, 153 were included, consisting of 4 clinical trials, 9 systematic reviews, 8 meta-analyses, and 5 longitudinal observational studies. The most recent national description of US malaria cases was available for 2017 at the time of this review.[2]

General Overview and Approach to the Diagnosis of Malaria

Malaria is caused by protozoa parasites of the genus *Plasmodium*. Female *Anopheles* mosquitoes acquire the parasites from an infected person during a blood meal and, on a subsequent human bite, transmit infection to a new host through the injection of sporozoites (**Figure 1**). The parasite infects hepatocytes and replicates until it becomes an exoerythrocytic merozoite, which enters the blood and invades erythrocytes. The intraerythrocytic trophozoite first appears as a ring form that undergoes morphologic changes during nuclear division as it develops into a schizont and subsequently ruptures the erythrocyte, releasing merozoites into the blood, repeating the erythrocytic infection cycle. The duration of the asexual intraerythrocytic life cycle varies and is 24 hours in *P knowlesi,* 72 hours in *P malariae,* and 48 hours in the other species. Some merozoites develop into sexual forms (gametocytes) and, when taken up by a mosquito during a blood meal, develop into sporozoites capable of transmitting infection into a new host. Rarely, infection occurs via vertical transmission during pregnancy or at birth, through blood transfusion, from needle sharing, or after an organ transplant from malaria-infected donors.[3,4] *P vivax* and *P ovale* also have a hypnozoite stage in the liver, which remains dormant for weeks to years before becoming activated into hepatic merozoites, entering the bloodstream, and initiating a blood-stage infection. The hypnozoite stage requires specific therapy, discussed later.

The diagnosis of malaria should be considered in a febrile patient returning from a malaria-endemic country (**Figure 2**).[5]

The amount of time that has elapsed between the date of arrival back to the US and symptom onset can provide a clue to the species. In 2017, 96.4% of patients infected with *P falciparum* became ill within 1 month after return to the US, whereas 47.5% of patients presenting with *P ovale* malaria became ill within 1 month after return (**Table 1**). Malaria is endemic in many regions of the world. Each species varies in geographic distribution and the number of infections caused within different regions. Patients can be infected with more than 1 species. In 2017, mixed-species infection accounted for 1.1% of reported cases in the US.[2] The region of travel can provide another indication to the likely infecting species.

The epidemiology of malaria diagnosed in the US reflects both the malaria-endemic regions where US travelers visit and the intensity of malaria transmission in those regions. In 2017, approximately 87.8% of patients with a diagnosis of malaria in the US acquired the infection in Africa,[2] whereas approximately 8.7% of cases were acquired in Asia, 1.8% from South America, 1.5% from Central America and the Caribbean, and less than 1.0% from Oceania.[2] Patients may not volunteer a history of travel. Therefore, clinicians evaluating patients with fever should inquire about travel to countries where malaria is endemic. Patients visiting friends and relatives living in an endemic area are at particularly high risk for acquiring malaria, and this group accounts for most of the malaria that is diagnosed in the US and other nonendemic countries.[2,6]

Long-term residents of malaria-endemic regions in high-transmission areas develop clinical immunity after repeated infections so that when they are infected they have mild to no symptoms. In contrast, most US travelers are not immune to malaria and are at risk for severe disease and death. US residents who had clinical immunity because of prior residence in a malaria-endemic region lose immunity over time after leaving the endemic region and become at risk for severe disease. Severe malaria is a medical emergency and is defined by World Health Organization criteria, which includes vital organ involvement consisting of shock, pulmonary edema, significant bleeding, seizures, and specific laboratory abnormalities (such as plasma lactate levels of ≥5 mmol/L or creatinine levels >3 mg/dL) (**Table 2**). In 2017, severe malaria affected approximately 14.4% of US travelers.[2] Patients with severe malaria should be hospitalized and receive intravenous artesunate therapy with close monitoring and supportive care (**Table 3**). Uncomplicated malaria, defined as infection in patients who do not have any criteria for severe malaria, can be treated with oral medication (Table 3).[7,8]

Symptoms of malaria are nonspecific and consist of fever, chills, headache, myalgia, nausea, vomiting, diarrhea, fatigue, abdominal pain, and altered mentation. Patients with malaria may initially have a misdiagnosis of a viral illness. In a case series of 95 patients, 13% of adult travelers who had returned to the US with malaria were misdiagnosed at initial presentation.[9] Once malaria is diagnosed, identification of the malaria species is necessary to select the appropriate antimalarial treatment (Table 3). Region of travel, length of time between return to the US and symptom onset, microscopy appearance, and a malaria rapid diagnostic test can help identify the species (Table 1).

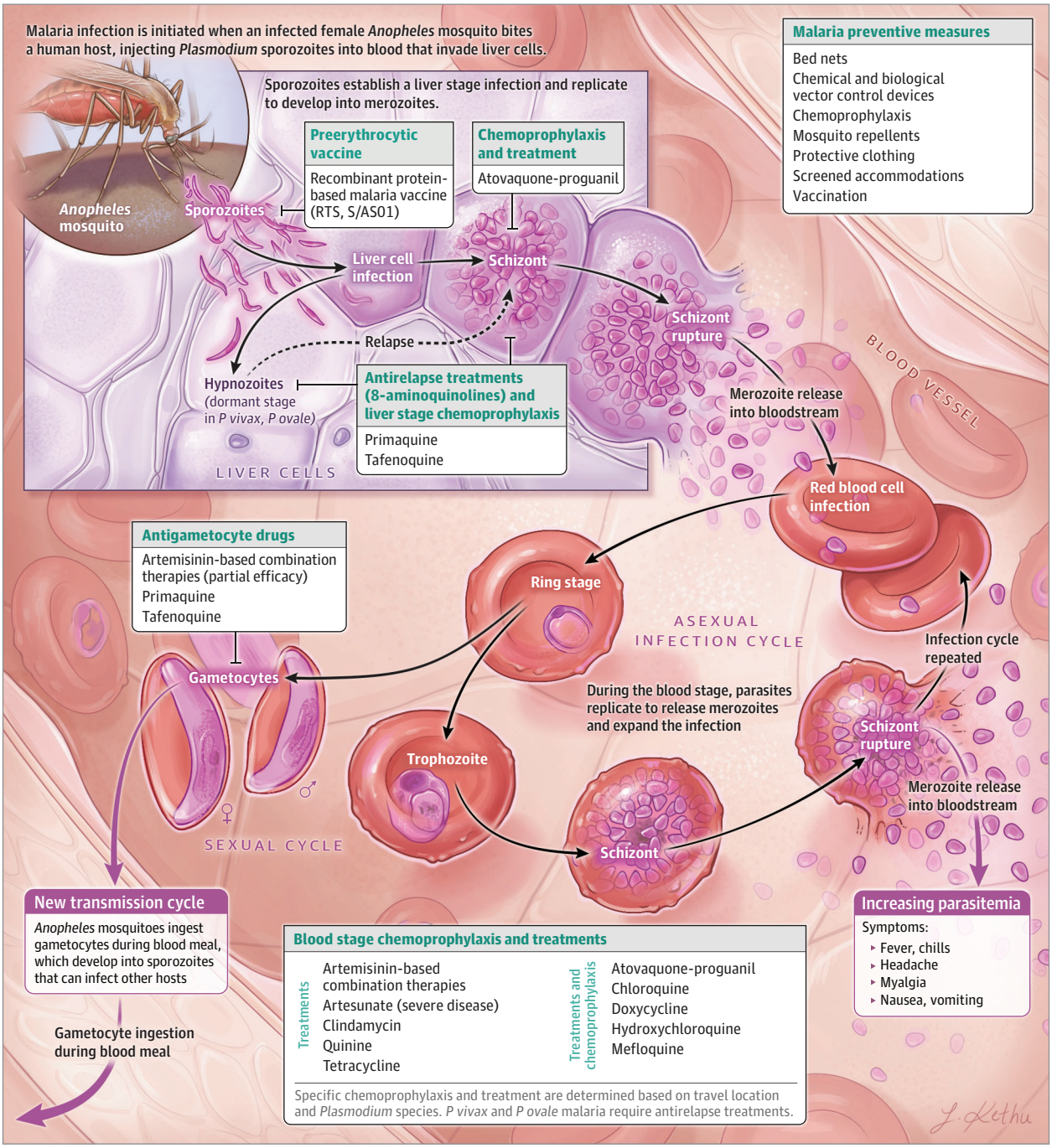
Delay in diagnosis or inappropriate treatment of malaria is associated with increased mortality due to malaria in the US. Prompt diagnosis, assessment of disease severity, and appropriate treatment are required.[2,10]

Malaria Species

P falciparum

P falciparum is the most common malaria species diagnosed in the US and accounted for 78.7% of malaria cases diagnosed in US travelers in 2017.[2] A total of 96.4% of US individuals infected with *P falciparum* in 2017 presented with symptoms within 1 month after arriving back in the US (Table 1).[2] Reactivation in immunosuppressed patients may occur years after travel, although the pathophysiology of persistent infection is not understood.[11] Microscopy shows early ring stages in infected erythrocytes of all sizes, frequently with multiple parasites in a single erythrocyte. In some patients, there is a high level of peripheral parasitemia. *P falciparum* can cause death rapidly in an individual without immunity. In 2017, death occurred in approximately 2.1% of patients with severe *P falciparum* malaria in the US. *P falciparum* was associated with all 6 US malaria-related deaths in 2017 and was associated with 5 of 7 deaths due to malaria in 2016.[2,10] Virulence of *P falciparum* is related to its ability to infect erythrocytes of all ages and sequestration of large numbers of late-stage infected erythrocytes in the microvasculature, which may contribute to a high pathogen

Figure 1. Schematic of *Plasmodium* Life Cycle and Stage-Specific Interventions



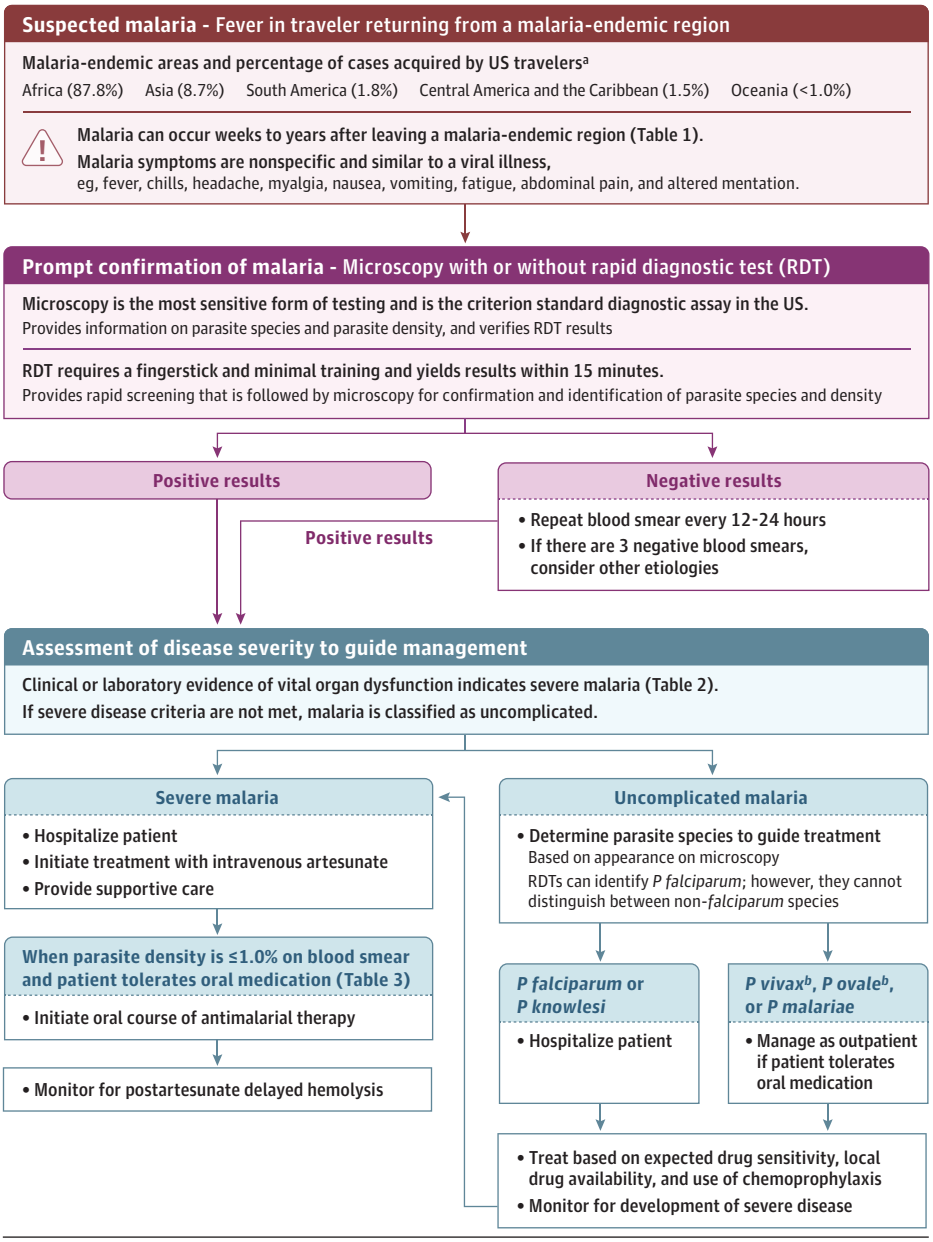
Malarial infection occurs after inoculation of sporozoites by an infected Anopheles mosquito during a blood meal. Sporozoites travel to the liver and establish a clinically silent infection, where the population undergoes massive expansion. Merozoites are released by the liver, invade red blood cells, and cause disease. A subset of blood-stage parasites becomes gametocytes to continue the transmission cycle after a subsequent blood meal. *P vivax* and *P ovale* can have a prolonged liver-stage infection (hypnozoite) that requires targeted therapy.

burden. Criteria for severe disease (Table 2) should be reviewed in every patient at hospital admission and reevaluated during the course of hospitalization because stable patients can subsequently deteriorate (Figure 2).

P vivax

In 2017, *P vivax* accounted for approximately 11.2% of malarial infection occurring in the US. An estimated 59% of returning US travelers developed symptoms within 1 month of travel.[2] *P vivax*

Figure 2. Evaluation for Returning Travelers With Fever From Malaria-Endemic Regions



Travelers returning from a malaria-endemic region with fever should always be tested for malaria using diagnostic assays. Severe disease requires prompt treatment and inpatient management, while uncomplicated disease may be managed as an outpatient in select settings.

[a] Data from *MMWR*.[2]

[b] *P vivax* and *P ovale* infections require treatment for the hypnozoite stage with an 8-aminoquinolone.

is endemic in Latin America and is also found in regions where *P falciparum* is endemic, with a few exceptions, such as Haiti.[2,12] Among travelers returning to the US with malaria in 2017, common regions of *P vivax* acquisition were Asia (63.5%), Africa (16.4%), South America (13.9%), Central America and the Caribbean (4.3%), and Oceania (1.9%).[2] *P vivax* preferentially invades reticulocytes (large, young erythrocytes), and therefore the maximal peripheral blood parasite load is rarely greater than 2% because of the low number of circulating reticulocytes. Unlike *P falciparum*, vascular sequestration does not occur, although recent studies have reported an abundance of intact *P vivax* in the spleen of people living in endemic areas, suggesting the possibility of an endosplenic life cycle in patients with chronic *P vivax* infection.[13]

Microscopy of blood smears reveals infection of reticulocytes with Schüffner dots, which are fine, red dots scattered throughout the cytoplasm. Early ring stage or later-stage ameboid trophozoite forms can be seen. Severe vivax malaria, diagnosed in 5.5% of patients with *P vivax* in 2017, is defined as falciparum malaria (Table 2) but without parasite density thresholds. Severe vivax malaria manifests as severe anemia, jaundice, respiratory distress, impaired consciousness, and kidney failure.[2,14,15] In 2016, severe *P vivax* malaria was associated with 2 deaths (28%) in US travelers.[10]

P vivax malaria can also arise from hypnozoite-stage parasites weeks to years after an individual leaves an endemic area and cause illness. A relapse of *P vivax* malaria can also occur weeks to years after treatment of the primary illness with chloroquine or artemisinin combination therapy (ACT). Malaria treatment regimens do not eradicate hypnozoites, which can reactivate and cause malaria.[16] Targeted therapy with 8-aminoquinolines is required to eradicate hypnozoites (**Box**).

Table 1. Characteristics of Malaria Species Infections

Plasmodium species	Incubation period, d	No. of days between arrival to US and onset of symptoms (%)[a]		Hypnozoite stage	Geographic distribution
		<30 d	≥365 d		
P falciparum	9-14	96.4	0.1	No	Sub-Saharan Africa, South and Southeast Asia, Eastern Mediterranean, Western Pacific, South America
P vivax	12-17 Relapse: 6-12 mo (>2 y in some cases)	59.5	1.4	Yes	Similar to *P falciparum* and also present in the Korean Peninsula
P ovale	16-18 Relapse: 8-45 mo	47.5	7.5	Yes	Sub-Saharan Africa, Southeast Asia, Western Pacific
P malariae	18-40 Persistence for decades	54.8	0	No	South America, Asia, Africa
P knowlesi	9-12	No data	No data	No	Southeast Asia

[a] Data from *MMWR*.[2]

Table 2. Diagnostic Criteria for Severe Disease[a]

Plasmodium species	Criteria	
	Signs and symptoms	Laboratory and radiology
P falciparum	Impaired consciousness: Glasgow Coma Scale score <11	Acidosis: base deficit of >8 mEq/L or plasma bicarbonate <15 mEq/L or venous plasma lactate ≥5 mmol/L
	Multiple convulsions: >2 seizures within 24 h	Anemia: hemoglobin concentration <7 g/dL or hematocrit <20% with a parasite count >10 000/μL
	Prostration: unable to sit, stand, or walk without assistance	Hypoglycemia: blood or plasma glucose <40 mg/dL
	Significant bleeding: recurrent or prolonged bleeding from the nose, gums, or venipuncture sites; hematemesis or melena	Parasitemia: ≥5%
	Shock: circulatory collapse/shock	Jaundice: plasma or serum bilirubin >3 mg/dL and parasite count >100 000/μL
		Kidney impairment: plasma or serum creatinine >3 mg/dL or blood urea nitrogen >56 mg/dL
		Pulmonary edema: radiologically confirmed or oxygen saturation <92% on room air with a respiratory rate >30/min
P vivax	Defined as for falciparum malaria but with no parasite density thresholds	
P knowlesi	Defined as for falciparum malaria except as below	
	P knowlesi parasite density >100 000/μL	
	Jaundice and parasite density >20 000/μL	

SI conversion factors: To convert plasma glucose to mmol/L, multiply by 0.0555; plasma or serum bilirubin to μmol/L, multiply by 17.104; plasma or serum creatinine to μmol/L, multiply by 88.4; and urea nitrogen to mmol/L, multiply by 0.357.

[a] Severe malaria can rarely occur in *P ovale* and *P malariae*, with no parasite density thresholds.

P ovale, *P malariae*, and *P knowlesi*

P ovale is endemic in sub-Saharan Africa and Asia and accounted for 6.2% of cases imported into the US in 2017, with approximately 47.5% of travelers presenting with symptoms within 1 month of travel.[2] *P ovale* includes 2 subspecies, *P ovale wallikeri* and *P ovale curtisi*, which have modest differences in latency period and effect on platelet and leukocyte counts.[17] Similar to *P vivax*, *P ovale* preferentially invades young red blood cells and is associated with low levels of peripheral blood parasitemia. Infected erythrocytes appear oval with fimbriae and Schüffner dots on microscopy. In a meta-analysis of 1365 patients infected with *P ovale* worldwide, severe *P ovale* affected approximately 0.03% (95% CI, 0.03%-0.05%).[18] *P ovale* has a hypnozoite stage and patients can present weeks to years after returning to the US or can relapse after treatment of a blood-stage infection. Therefore, *P ovale* infection requires medications that are active against the liver hypnozoites to prevent illness.

P malariae is associated with low levels of peripheral parasitemia because it invades only aged erythrocytes, which are uncommon in blood. *P malariae* accounted for only 2.8% of all malarial infections in US travelers in 2017, and 54.8% of those with a diagnosis of *P malariae* presented within 1 month of travel.[2] *P malariae* does not have a hypnozoite stage; however, it can cause illness months to years after the patient has left the endemic region. Rarely, severe disease can occur, and in a meta-analysis of 10 520 patients infected with *P malariae*, the pooled prevalence estimate of severe malarial infection was 3% (95% CI, 2%-5%).[19] Severe disease presented typically as severe anemia, pulmonary complications, and kidney impairment.[19]

Table 3. Treatment of Malaria[a]

Malaria species	Drug	Regimen	Adverse reactions (frequency, %)[b]
Severity: uncomplicated malaria			
P falciparum or unknown			
Preferred treatment	Artemether-lumefantrine (Coartem) (1 tablet: 20 mg artemether + 120 mg lumefantrine)[c]	Day 1: 4 tablets by mouth once and then at 8 h Days 2, 3: 4 tablets by mouth twice daily	Headache (56), anorexia (40), dizziness (39), asthenia (38)
Alternative treatments	Atovaquone-proguanil (1 tablet: 250 mg atovaquone + 100 mg proguanil)[d]	4 Tablets by mouth daily for 3 d	Abdominal pain (17), nausea/vomiting (12), headache (10)
	Quinine sulfate[e] plus doxycycline, tetracycline, or clindamycin[e]	Quinine sulfate: 542-mg base (650-mg salt) by mouth 3 times daily for 3-7 d plus 1 of the following	"Cinchonism" (eg, headache, vision disturbances, sweating)[f]
		Doxycycline, 100 mg by mouth twice daily for 7 d	Esophageal ulcers (<1), sunburn (>10), diarrhea (5)
		Tetracycline, 250 mg by mouth 4 times daily for 7 d	Photosensitivity, abdominal discomfort, nausea, vomiting
		Clindamycin, 20 mg/kg/d by mouth divided 3 times daily for 7 d	Diarrhea, *Clostridioides difficile* colitis, hypersensitivity
	Mefloquine[e]	Base at 684 mg (750-mg salt) by mouth once; then second dose of 456-mg base (500-mg salt) by mouth at 6-12 h	Vomiting (3), neuropsychiatric effects, dizziness
	Chloroquine phosphate (if chloroquine sensitive) (Aralen and generics)[e]	Base at 600 mg (1000-mg salt) by mouth once; then 300-mg base (500-mg salt) by mouth at 6, 24, and 48 h	Visual disturbances, nausea and vomiting, pruritus
	Hydroxychloroquine (if chloroquine sensitive) (Plaquenil and generics)[e]	Base at 620 mg (800-mg salt) by mouth once; then 310-mg base (400-mg salt) by mouth at 6, 24, and 48 h	QT prolongation, neuropsychiatric effects, abnormal liver function test results
P vivax or *P ovale*			
Chloroquine sensitive			
Acute treatment	Chloroquine (Aralen and generics)[e]	Base at 600 mg (1000-mg salt) by mouth once; then 300-mg base (500-mg salt) by mouth at 6, 24, and 48 h	Visual disturbances, nausea and vomiting, pruritus
	Hydroxychloroquine (Plaquenil and generics)[e]	Base at 620 mg (800-mg salt) by mouth once; then 310-mg base (400-mg salt) by mouth at 6, 24, and 48 h	QT prolongation, neuropsychiatric effects, abnormal liver function test results
Plus antirelapse treatment[g]	Primaquine phosphate	Base at 30 mg by mouth daily for 14 d	Hemolytic anemia in G6PD deficiency, nausea, vomiting
	Tafenoquine (Krintafel)[h]	1 Dose at 300 mg by mouth	Diarrhea (18), headache (15), hemolytic anemia in G6PD deficiency (<1), vortex keratopathy (21-93)
Chloroquine resistant (Papua New Guinea, Indonesia)			
Acute treatment	Artemether-lumefantrine (Coartem) (1 tablet: 20 mg artemether + 120 mg lumefantrine)[c]	Day 1: 4 tablets by mouth once and then at 8 h Days 2, 3: 4 tablets by mouth twice daily	Headache (56), anorexia (40), dizziness (39), asthenia (38)
	Atovaquone-proguanil (Malarone) (1 tablet: 250 mg atovaquone + 100 mg proguanil)[d]	4 Tablets by mouth daily for 3 d	Abdominal pain (17), nausea/vomiting (12), headache (10)
	Quinine sulfate[e] plus doxycycline, tetracycline, or clindamycin[e]	Quinine sulfate: 542-mg base (650-mg salt) by mouth 3 times daily for 3-7 d plus 1 of the following:	"Cinchonism" (eg, headache, vision disturbances, sweating)[f]
		Doxycycline, 100 mg by mouth twice daily for 7 d	Esophageal ulcers (<1), sunburn (>10), diarrhea (5)
		Tetracycline, 250 mg by mouth 4 times daily for 7 d	Photosensitivity, abdominal discomfort, nausea, vomiting
		Clindamycin, 20 mg/kg/d by mouth divided 3 times daily for 7 d	Diarrhea, *Clostridioides difficile* colitis, hypersensitivity
	Mefloquine[e]	Base at 684 mg (750-mg salt) by mouth once; then 456-mg base (500-mg salt) by mouth at 6-12 h	Vomiting (3), neuropsychiatric effects, dizziness
Plus antirelapse treatment[g]	Primaquine phosphate	Base at 30 mg by mouth daily for 14 d	Hemolytic anemia in G6PD deficiency, nausea, vomiting

(continued)

P knowlesi is a zoonotic parasite of macaques that is endemic in Southeast Asia but infrequent in travelers returning to the US.[20] Similar to *P falciparum,* this species can cause high parasite loads, severe malaria, and death. In contrast to *P falciparum,* coma does not occur.[21] Initially, *P knowlesi* was frequently misdiagnosed as *P malariae* because the trophozoites shared common features on microscopy. In a case series of deaths due to *P knowlesi,* 69% of deaths were incorrectly identified as being caused by *P malariae*.[22] Deaths due to *P knowlesi* were commonly associated with respiratory distress, jaundice, and acute kidney injury. Severe disease is defined as for falciparum malaria, however with different parasitemia cutoffs, which are parasite density greater than 100 000/μL or jaundice and parasite density greater than 20 000/μL (Table 2).[14]

Table 3. Treatment of Malaria[a] (continued)

Malaria species	Drug	Regimen	Adverse reactions (frequency, %)[b]
P malariae or *P knowlesi*			
All regions (no known resistance)			
	Chloroquine (Aralen and generics)[e]	Base at 600 mg (1000-mg salt) by mouth; then 300-mg base (500-mg salt) by mouth at 6, 24, and 48 h	Visual disturbances, nausea and vomiting, pruritus
	Hydroxychloroquine (Plaquenil and generics)[e]	Base at 620 mg (800-mg salt) by mouth; then 310-mg base (400-mg salt) by mouth at 6, 24, and 48 h	QT prolongation, neuropsychiatric effects, abnormal liver function test results
	Artemether-lumefantrine (Coartem) (1 tablet: 20-mg artemether + 120-mg lumefantrine)[c]	Day 1: 4 tablets by mouth once and then at 8 h Days 2, 3: 4 tablets by mouth twice daily	Headache (56), anorexia (40), dizziness (39), asthenia (38)
	Atovaquone-proguanil (Malarone) (1 tablet: 250-mg atovaquone + 100-mg proguanil)[d]	4 Tablets by mouth daily for 3 d	Abdominal pain (17), nausea/vomiting (12), headache (10)
	Quinine sulfate[e] plus doxycycline, tetracycline, or clindamycin[e]	Quinine sulfate: 542-mg base (650-mg salt) by mouth 3 times daily for 3-7 d plus 1 of the following:	"Cinchonism" (eg, headache, vision disturbances, sweating)[f]
		Doxycycline, 100 mg by mouth twice daily for 7 d	Esophageal ulcers (<1), sunburn (>10), diarrhea (5)
		Tetracycline, 250 mg by mouth 4 times daily for 7 d	Photosensitivity, abdominal discomfort, nausea, vomiting
		Clindamycin, 20 mg/kg/d by mouth divided 3 times daily for 7 d	Diarrhea, *Clostridioides difficile* colitis, hypersensitivity
	Mefloquine[e]	Base at 684 mg (750-mg salt) by mouth once; then 456-mg base (500-mg salt) by mouth at 6-12 h	
Severity: severe malaria			
All species	Initial therapy: IV artesunate[i]	IV at 2.4 mg/kg at 0, 12, and 24 h Reassessment: unable to take oral medication or parasite density >1%: continue IV artesunate, same dose, daily up to 7 d until parasite density ≤1% When parasite density ≤1%, give full course of an oral regimen	Acute kidney failure (8.9), jaundice (2.3), hemoglobinuria (6.7)

Abbreviations: G6PD, glucose-6-phosphate dehydrogenase; IV, intravenous.

[a] Adapted from the Centers for Disease Control and Prevention.[7]

[b] Adverse reactions are based on product label by the US Food and Drug Administration (FDA). Frequencies of adverse events for select drugs have not been defined by the FDA.

[c] May be given in second and third trimesters in pregnant individuals.

[d] Contraindicated in pregnancy unless no other treatment options are available.

[e] May be given in all trimesters.

[f] Adverse effect occurs in almost all patients taking this medication.

[g] During pregnancy, give chloroquine 300-mg base (500-mg salt) weekly until delivery and then treat with primaquine or tafenoquine to prevent relapse if no contraindications.

[h] Tafenoquine is not effective to prevent recurrence if active infection treated with nonchloroquine regimen.

[i] After initial therapy, complete a full oral regimen. If IV artesunate is not readily available, give oral regimen while obtaining IV artesunate. Concomitant use with ritonavir, nevirapine, or carbamazepine may decrease serum concentrations of the active metabolite dihydroartemisinin and the efficacy of artesunate.[8]

Diagnosing Malaria

Laboratory tests are necessary to confirm the diagnosis of malaria. If tests are not available, the patient should promptly be referred to a facility with diagnostic capabilities (Figure 2).

Microscopy

Microscopy is the criterion standard for diagnosis of malaria in the US. It involves analyzing a drop of blood on thick and thin Giemsa-stained blood films and requires an experienced microscopist. Thick smears allow the analysis of a greater number of red blood cells and are more sensitive in detecting parasites. Thin smears provide speciation and quantification and can be prepared more rapidly for inspection compared with thick smears. Three blood smears should be obtained every 12 to 24 hours to establish the diagnosis of malaria. All species have a similar appearance in the early ring stage, and distinguishing between species may be difficult, particularly when the level of parasitemia is low. In a meta-analysis of 8079 patients with malaria, *P ovale* was misidentified as *P vivax* malaria during microscopy in 11% (95% CI, 7%-14%) of diagnoses compared with the criterion standard of polymerase chain reaction.[23] When there is a high degree of suspicion for malaria in a patient with manifestations of severe disease with a negative smear, it is reasonable to empirically initiate therapy, obtain additional smears, and rule out other etiologies of illness (Figure 2).

A parasitemia level of at least 5% for *P falciparum* defines severe disease, although travelers without immunity may have severe disease with a lower peripheral parasite load. The Centers for Disease Control and Prevention (CDC) recommends that after initiation of treatment for *P falciparum*, *P knowlesi*, or suspected chloroquine-resistant *P vivax* malaria, blood smear testing should be repeated every 12 to 24 hours to confirm a therapeutic response, defined as a decline in parasitemia level. In all patients, a negative smear result should be documented after treatment. Infection with more than 1 species can occur and careful inspection of the blood smear is necessary to rule out coinfection.[2] All laboratory-confirmed cases should be reported to the state health department.

Rapid Diagnostic Tests

Rapid diagnostic tests are a complementary diagnostic test, provide a rapid result, and require minimal training. They are often used in US health care systems to screen patients, followed by microscopy, which can confirm the rapid diagnostic test result, identify the species, and quantify the parasitemia level.

The BinaxNOW malaria test (Abbott Laboratories) is the only Food and Drug Administration (FDA)–approved rapid diagnostic test. It is an immunochromatographic assay that uses monoclonal antibodies to detect the presence of *P falciparum*–specific histidine-rich protein II and a panmalarial antigen common to all species except for *P knowlesi* from a blood sample.[24] This test can determine whether *P falciparum* is present in the blood, with 99.7% sensitivity and 94.2% specificity for parasitemia levels greater than 5000 parasites per microliter. False-negative results can occur for *P falciparum* strains with deletions in the target HRP2 protein.[25,26] This FDA-approved rapid diagnostic test can detect *P falciparum*; however, it cannot distinguish between *P vivax*, *P ovale*, and *P malariae*. RDTs have a lower sensitivity for nonfalciparum species because these parasites typically are associated with low peripheral blood parasite levels. With an experienced microscopist, the limit of detection can be up to 5 to 10 parasites per microliter, whereas the limit of detection of the rapid diagnostic test is 1001 parasites per microliter for *P falciparum* and 5001 for *P vivax*; thus, microscopy is more sensitive than rapid diagnostic tests in the case of low-level parasitemia.[27] The Food and Drug Administration requires that the rapid diagnostic test results be confirmed by the more sensitive thick and thin microscopy. Rapid diagnostic test results remain positive after treatment and cannot be used to monitor response to antimalarial therapy.[28]

Box. Commonly Asked Questions About Malaria

What Are Typical Signs and Symptoms of Malaria?

Patients with malaria typically present with symptoms that resemble an influenzalike illness. Common symptoms are fever, headache, myalgia, diarrhea, and shortness of breath. Severe malaria can present with symptoms of confusion and dyspnea. Because the symptoms of malaria are nonspecific, patients should be asked about travel to areas with endemic malaria. Clinicians should promptly order a malaria diagnostic test whenever malaria is a possible diagnosis.

Why Is Chemoprophylaxis Continued After Patients Return to the US After Travel to the Endemic Area?

Plasmodium falciparum, which has the highest mortality of the malaria species, typically causes symptoms within 4 wk after return from the endemic area due to parasites entering the bloodstream from the liver during this period. To maintain adequate blood levels of preventive therapy for a month, chloroquine, mefloquine, and doxycycline are continued for 1 mo after return to the US. Atovaquone-proguanil, primaquine, and tafenoquine can eradicate the liver stage, and thus therapy is continued for 1 wk after return to the US. It is important to educate patients to adhere to the preventive regimen after returning to the US to prevent malaria.

What Is the Best Way to Obtain a Laboratory Diagnosis of Malaria?

Microscopy remains the criterion standard to diagnose malaria. It can indicate the species, quantify the parasitemia level, and requires microscopy expertise. The BinaxNOW malaria test is the only Food and Drug Administration–approved rapid diagnostic test and is useful while microscopy results are awaited. Rapid diagnostic tests achieve a more rapid result, can serve as a point-of-care test, and are useful if the microscopist is unavailable, such as during evening hours. The rapid diagnostic test result must be confirmed by microscopy, which is a more sensitive test and provides additional information, such as species, to inform treatment.

Prevention and Treatment of Malaria

Prevention of Malaria

A detailed travel itinerary should be obtained to determine whether a patient is likely to be exposed to infectious mosquitoes. The CDC website provides country-specific information on the risk of malaria and recommended prophylaxis. In areas of high risk, personal protective measures should be used to prevent malarial infection, including mosquito repellents, protective clothing, bed nets, screened accommodations, and vector control devices.[29] Chemoprophylaxis can prevent infection and should be prescribed for individuals traveling to endemic areas. The ideal agent depends on whether the region has chloroquine-sensitive or -resistant malaria, drug adverse event profile, frequency of dosing, and patient preference (**Table 4**).[30]

Among US residents who developed malaria in 2017, 93% either did not use or did not adhere to a CDC-recommended chemoprophylaxis regimen.[2] Patients should be educated about malarial chemoprophylaxis and the importance of adherence to preventive therapy. Patients visiting friends and relatives, which constituted 50% of those with malaria in 2017, may have partial immunity to malaria because of exposures during prior residence in malaria-endemic regions. However, these patients are at risk for disease and death and should receive prophylaxis. Other barriers to chemoprophylaxis include availability of drugs and high costs, which are not always covered by health insurance.[31] Malarial infection can occur after chemoprophylaxis. For example, 42 cases of *P falciparum* and 5 cases of *P malariae* occurred in 2017 among patients who reported complete adherence to a CDC-recommended chemoprophylaxis regimen.[2]

The *P falciparum* malaria vaccine, RTS,S/ASO1, is a recombinant protein-based subunit vaccine that targets the sporozoite and liver stages to prevent blood-stage disease. It was approved by the World Health Organization in October 2021 for widespread use among children living in malaria-endemic countries.[32] Vaccine efficacy was 46% (95% CI, 42%-50%) against clinical malaria in African children during the 18 months after vaccination and 34% (95% CI, 15% to 48%) against severe malaria, malaria hospitalization, and all-cause hospitalization.[33] This vaccine is not approved for use in travelers because its efficacy has not been studied in residents of nonendemic regions.

Management of Uncomplicated Malaria

All uncomplicated *P falciparum* malaria can be treated with ACTs regardless of chloroquine sensitivity.[14] If ACTs are unavailable, a non-ACT can be used for chloroquine-resistant malaria such as atovaquone-proguanil or quinine plus clindamycin (Table 3). In patients with known chloroquine-sensitive *P falciparum*,

Table 4. Malaria Chemoprophylaxis by Dosing Frequency

Drug	During travel		Pretravel	Posttravel	Adverse events (frequency, %)
	Daily	Weekly			
Atovaquone/proguanil (250 mg/100 mg)	X		Daily for 1-2 d before travel	Daily, 7 d	Nausea/vomiting (12)
Doxycycline (100 mg)	X		Daily, 1-2 d	Daily, 30 d	Esophageal ulcers (<1), sunburn (>10)
Primaquine (30-mg base)[a,b]	X		Daily, 1-2 d	Daily, 7 d	G6PD deficiency–associated anemia
Chloroquine (300-mg base)		X	Weekly, 1-2 wk	Weekly, 4 wk	Nausea/vomiting
Mefloquine (228-mg base)		X	Weekly, 1-2 wk	Weekly, 4 wk	Neuropsychiatric (14)
Tafenoquine (200 mg)[c,d]		X	Daily, 3 d	Weekly, 7 d	G6PD deficiency–associated anemia

Abbreviation: G6PD, glucose-6-phosphate dehydrogenase.

[a] Primaquine is most effective in areas with greater than 90% *Plasmodium vivax*.

[b] Primaquine and tafenoquine may be used as postexposure prophylaxis in travelers to *P vivax*– or *P ovale*–endemic areas.

[c] Tafenoquine is Food and Drug Administration approved for chemoprophylaxis.

[d] Frequency of adverse event is not defined by the Food and Drug Administration.

such as in Haiti, chloroquine remains a good treatment option. If patients were receiving chemoprophylaxis and develop a malarial infection, the treatment regimen should be an alternative antimalarial therapy unless no other options are available. There have been reports of reduced efficacy of artemisinin-lumefantrine for patients with *P falciparum* malaria and high body mass index. Among 61 patients with *P falciparum*, the effectiveness of artemisinin-lumefantrine was 100% (95% CI, 66.4%-100%) in subjects weighing 65 kg or less and 90.4% (95% CI, 79.0%-96.8%) in those weighing more than 65 kg.[34] Patients, including those with high body mass index, should be aware of possible relapse after treatment and, if symptoms recur, promptly seek medical care. *P falciparum* malaria relapse could also be due to drug resistance. Artemisinin-resistant malaria now affects patients with malaria in parts of Cambodia, the Lao People's Democratic Republic, Myanmar, Thailand, Vietnam, Rwanda, Uganda, and Amazonia.[14,35-37] In an open-label trial of 1241 subjects in western Cambodia, where artemisinin-based combination therapies were failing, efficacy of a 6-day course of antimalarial therapy was associated with a cure rate of 97.7% (95% CI, 90.9% to 99.4%) at 42 days.[38] Thus, treatment of artemisinin-resistant malaria may require an alternative therapy with atovaquone-proguanil or 6 days of ACT therapy (Table 3). Consultation with experts through the CDC Malaria Hotline can provide guidance for the evaluation and treatment of suspected drug-resistant malaria.

P vivax, P ovale, P malariae, and *P knowlesi* are typically chloroquine sensitive, and the World Health Organization recommends treatment with either ACT (except for pregnant individuals in their first trimester) or chloroquine for regions with chloroquine-susceptible infections for uncomplicated malaria.[14]

In regions with *P vivax* chloroquine resistance, including in Papua New Guinea, Indonesia, and Oceania, and where chloroquine failure exceeds 10% at day 28 posttherapy, ACT should be used instead of chloroquine.[14,39] Microscopic detection of parasites at 48 hours after chloroquine treatment in *P vivax* is associated with chloroquine resistance, and for these patients, ACT should be considered for treatment.[40]

Treating Severe Malaria

Patients with severe malaria must receive rapid diagnosis and treatment. Severe disease is defined by World Health Organization criteria (Table 2). In 2017, severe disease in US travelers presented as parasitemia of at least 5% (68.8%), acute kidney injury (15.1%), cerebral malaria (10.6%), acute respiratory distress syndrome (8.0%), severe anemia (4.2%), and jaundice (3.9%).[2] Intravenous artesunate is the drug of choice for severe malaria and is now available commercially.[41] It should be administered for at least 3 doses. Once the parasite density is 1% or less and the patient is able to take medications by mouth, a full oral treatment course of ACT is administered. A study of 170 US patients with severe malaria reported that 93.5% achieved parasitemia at 1% or less by the third dose of intravenous artesunate.[42] A potential adverse effect of artesunate is post-artemisinin delayed hemolysis, defined as a 10% or greater decrease in hemoglobin levels with haptoglobin less than 0.1 g/L and an increase of lactate dehydrogenase to greater than 390 U/L, or an increase of at least 10% over values from presentation occurring at least 7 days after initiation of intravenous artesunate. Postartemisinin delayed hemolysis occurred in 4.8% of 280 US patients presenting 1 to 3 weeks after treatment.[42] Patients should be monitored for this adverse event for 4 weeks posttherapy[8]; rare case reports after oral therapy for treatment of severe falciparum malaria with ACTs have been described.[43,44] Intravenous quinidine is no longer available for treatment in the US.

A retrospective review of 21 travelers who presented to a metropolitan tertiary care hospital with severe malaria between 2000 and 2017 reported 100% survival; however, between 2016 and 2017, 13 deaths were reported nationally.[2,10,45] Contrary to treatment guidelines, 30.4% of patients with severe malaria in 2017 were treated with an oral antimalarial regimen.[2] Hospital pharmacies should consider stocking artemisinin, particularly in regions where malaria is common and this may increase its rate of use for severe disease. Alternatively, emergency procurement of artemisinin can be sought. If there is a delay in obtaining artemisinin, oral antimalarials should be administered while intravenous artesunate is awaited.

Levels of blood glucose, hematocrit, parasitemia, and plasma bicarbonate, as well as kidney function, should be monitored in severe malaria. Excessive intravenous fluids could potentially worsen pulmonary or cerebral edema. Restrictive fluid management did not worsen kidney function or tissue perfusion.[46] Blood cultures should be obtained to identify a concomitant bacterial infection, and antibiotics should be initiated if bacterial superinfection is suspected, particularly in the setting of hypotension.[14]

Acute kidney injury is common in severe malaria, and creatinine and urine output should be monitored daily.[47] A phase 2

open-label randomized controlled trial of 62 adults in Bangladesh who had severe falciparum malaria and received acetaminophen (paracetamol) found a greater median proportional reduction in serum creatinine level at 72 hours compared with the value at study enrollment (23%; IQR, 18%-37%) compared with patients who did not receive acetaminophen (14%; IQR, 0%-29%; $P = .04$), suggesting a beneficial effect of acetaminophen on restoring kidney function.[48] Acetaminophen may reduce heme-ferryl radical–mediated kidney damage, and clinical trials are ongoing to study its efficacy as a preventive therapy.

Cerebral malaria is an encephalopathy due to malaria, with a complex pathophysiology and a mortality rate of approximately 15% to 20%. It is often associated with cerebral edema, seizures, and other vital organ involvement. Pipecolic acid, a neuromodulatory molecule produced by *Plasmodium* parasites, was elevated in the plasma of 35 patients with cerebral malaria compared with 10 with mild malaria, suggesting a possible mechanism of coma.[49] Alternative etiologies of coma, including hypoglycemia and meningitis, should be ruled out. Lumbar puncture was safe in 866 patients with cerebral malaria and neuroimaging should be obtained as indicated.[50] Cerebral edema can develop in cerebral malaria and supportive care should be administered.[51] In an open-label randomized trial of 60 patients with cerebral malaria, median time to recovery from coma was 90 hours (range, 22-380 hours) with mannitol vs 32 hours (range, 5-168 hours) without ($P = .02$) and was associated with higher mortality (30% vs 13%) compared with the no adjunctive therapy arm.[52] More than 32 randomized clinical trials to test adjunctive therapies, such as dexamethasone, inhaled nitric oxide, and anti–tumor necrosis factor monoclonal antibody to improve outcomes in severe malaria, have been conducted and none have demonstrated beneficial effects.[53]

Exchange blood transfusion, in which the patient's blood is removed and replaced by donated blood, has not been demonstrated to improve outcomes.[54,55] The World Health Organization makes no recommendation for its use in severe malaria and the CDC does not recommend its use.[14]

Treating Hypnozoites in *P ovale* and *P vivax*

P vivax and *P ovale* hypnozoites can reactivate to cause malaria weeks to years after an individual leaves the endemic area (Figure 1). The biology of hypnozoites is unique and antimalarial therapies are ineffective for hypnozoite eradication. Primaquine and tafenoquine are 8-aminoquinolines that can eradicate hypnozoites to prevent relapse. Activity of glucose-6-phosphate dehydrogenase (G6PD) must be measured before the agent's prescription because it can cause hemolysis in the setting of G6PD deficiency. Primaquine requires 2 weeks of oral therapy in contrast to tafenoquine, which requires a single dose.[56] Tafenoquine has 2 formulations: Krintafel (GlaxoSmithKline) for hypnozoite eradication and Arakoda (Sixty Degrees Pharma) for primary chemoprophylaxis for all species of malaria.[30] Randomized clinical trials as part of multicenter, international trials demonstrated the benefit of a single dose of tafenoquine comparable to 2 weeks of primaquine to prevent recurrent *P vivax* malaria.[57,58] Tafenoquine can be used after successful chloroquine treatment of the blood stage and is not approved for use with other antimalarial treatment regimens.[59] Tafenoquine is contraindicated in patients with G6PD deficiency (<70% enzymatic function), during pregnancy, and in parents breastfeeding infants with unknown G6PD status.[60] For patients with G6PD deficiency, primaquine (45-mg base) by mouth can be administered for 8 weeks with close monitoring for hemolysis and consultation of an expert in infectious diseases.[61]

Pregnant Individuals and Malaria

Malarial infection during pregnancy can cause fetal loss, low birth weight, or congenital infection.[62] Atovaquone-proguanil is contraindicated for use during pregnancy unless no other treatment options are available.[63] Tetracycline is contraindicated in breastfeeding mothers.

The treatment of uncomplicated chloroquine-resistant malaria during the first trimester is with 7 days of quinine plus clindamycin. Artemisinin combination therapies can be used to treat uncomplicated malaria in the second and third trimester. Tafenoquine and primaquine are contraindicated during pregnancy for preventing relapse of *P vivax* or *P ovale* malaria. After treatment of *P vivax* or *P ovale* malaria in pregnant and breastfeeding individuals, weekly chemoprophylaxis with chloroquine should be prescribed until delivery, followed by 2 weeks of primaquine or a single dose of tafenoquine, according to the patient's G6PD status.[14] Tafenoquine and primaquine should not be used in lactating parents, if the infant has G6PD deficiency, or if the G6PD status is unknown. Intravenous artesunate is the treatment of choice in all trimesters for severe malaria during pregnancy.[14] Congenital malaria was diagnosed in 2 patients in the US in 2017, and thus blood smears should routinely be obtained from the newborn when malarial infection was possible during pregnancy.[2]

The CDC provides resources for malaria management, including assessment for drug resistance. They are available through the CDC Malaria Hotline (https://www.cdc.gov/malaria/diagnosis_treatment/clinicians1.html).

Limitations

This review has several limitations. First, the quality of the included evidence was not evaluated. Second, some relevant studies may not have been included. Third, the review was limited to travelers returning to the US and may not be generalizable to other populations. Fourth, much of the evidence on incidence and characteristics of malaria comes from the 2017 CDC report, which provides the most current US data available at this time.[61]

Conclusion

Approximately 2000 cases of malaria are diagnosed each year in the US, most commonly in travelers returning from visiting endemic areas. Prevention and treatment of malaria depend on the species and the drug sensitivity of parasites from the region of acquisition. Intravenous artesunate is first-line therapy for severe malaria.

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