Malaria in Children

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KEYWORDS

• Malaria • *Plasmodium* • *Falciparum* • *Vivax*

KEY POINTS

- Malaria is a significant cause of morbidity and mortality in endemic areas.
- Travelers to endemic areas are at risk of malaria.
- Identifying patients who may have malaria and providing prompt evaluation and treatment are critical to limit disease and its complications.
- Malaria has the potential to be fatal. In cases where the index of suspicion is high, treatment can be started before testing results are available, so that there is no delay in therapy. If presumptive treatment is initiated, diagnostic specimens should still be obtained.
- Updated guidelines are available through the US Centers for Disease Control and Prevention and should be consulted whenever a physician is treating patients with suspected or confirmed malaria.

INTRODUCTION

Malaria causes substantial morbidity and mortality in many of the most resource-limited areas of the world. In addition, malaria is a threat to travelers to endemic areas and should be considered in the evaluation of any traveler returning from a malaria-endemic region presenting with fever. Malaria infection can rapidly develop into severe disease that can be fatal. Prompt, effective treatment is critical to limiting these complications. Understanding the species-specific epidemiology and drug-resistance patterns in the geographic area where infection was acquired guides treatment. This review contains an overview of the epidemiology and pathogenesis of malaria with a focus on components relevant to treating malaria in nonendemic areas. Guidance for treatment and management of malaria in returned travelers is provided.

CAUSE AND PATHOGENESIS

Malaria is caused by infection with *Plasmodium* parasites. Five species cause disease in humans: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*,

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Plasmodium ovale, and *Plasmodium knowlesi.* Infection is spread by the bite of a female *Anopheles* mosquito and has obligatory human and mosquito stages of the life cycle. The species of *Anopheles* mosquitoes responsible for *Plasmodium* transmission has a broad geographic distribution. Typically, *Anopheles* bite from dusk to dawn. However, exact biting patterns vary based on specific species.

The life cycle of the 5 *Plasmodium* species is similar, apart from the dormant stages of *P vivax* and *P ovale*:

- Sporozoites are inoculated into humans by an *Anopheles* mosquito and immediately invade hepatocytes.
- Asexual replication takes place initially in the liver, leading to the release of thousands of merozoites per infected hepatocyte into the blood. This release occurs 1 to 2 weeks after the bite of the infectious mosquito.
- Blood stage infection causes clinical disease.
- Merozoites invade erythrocytes, undergo asexual reproduction, and then rupture out of the erythrocyte, allowing the daughter merozoites to continue the cycle of invasion and replication.
- Some blood stage parasites develop into male and female gametocytes, the stage that is responsible for transmission to the mosquito.
- For the infection to be transmitted, a female *Anopheles* mosquito must ingest erythrocytes containing male and female gametocytes.
- Sexual reproduction takes place in the mosquito midgut where the gametocytes mature into gametes, merge to form a zygote, and then develop into an ookinete.
- Ookinetes invade the mosquito stomach wall and develop into oocysts, which rupture and release sporozoites.
- Sporozoites migrate to the mosquito salivary gland and may infect another human during the mosquito's next blood meal.
- Of note, in *P vivax* and *P ovale*, dormant stages, called hypnozoites, may remain quiescent in the liver of the infected human for weeks to years from the initial infection, leading to onset of clinical symptoms or relapses of infections much later. Treatment specifically targeting these dormant stages is required to completely clear infections with *P vivax* and *P ovale.*

Malarial disease results from multiple complex parasite-host interactions during the asexual, blood stage of infection. Clinical manifestations of disease are related to parasite modification of the erythrocyte and parasite-induced inflammation.

Plasmodium pathogenesis can be divided into inflammation, anemia, and end-organ damage. Inflammation is caused by the downstream effects of parasite metabolism and erythrocyte rupture, and, in *P falciparum*, parasite sequestration. Splenic macrophages and monocytes release large amounts of proinflammatory cytokines in response to phagocytosis of hemozoin, a toxic metabolite from the parasite digestion of heme, and other erythrocyte remnants. Proinflammatory cytokines in turn give rise to (1) the systemic inflammatory response syndrome, (2) edema and inflammation in perivascular tissues in end organs due to disruption of endothelial basal lamina and extravasation,[1] and (3) increased expression of adhesion molecules and increased sequestration of parasitized erythrocytes.

The anemia caused by *Plasmodium* infection is multifactorial. Asexual reproduction in infected erythrocytes leads directly to hemolysis. Moreover, intraerythrocytic parasites decrease erythrocyte deformability, leading to increased hemolysis and splenic clearance, compounded by splenic sequestration in *P falciparum* infection. Hematopoiesis, which would normally compensate for hemolysis, is suppressed by tumor necrosis factor-alpha released during infection.

End organ damage due to *P falciparum* infection is mediated by cytoadherence of infected erythrocytes, also referred to as sequestration. Intraerythrocytic parasites produce proteins that are expressed on the surface of infected erythrocytes and lead to binding to a variety of cell types. Binding of parasitized erythrocytes in the microvasculature along with uninfected erythrocytes, inflammatory cells, and platelets leads to partial blood flow obstruction, breakdown of the endothelium, and inflammation that causes end organ damage. Sequestered erythrocytes can be found in any organ. Sequestration in the brain leads to the clinical syndrome of cerebral malaria described in later discussion. Sequestration in the placenta leads to the adverse birth outcomes associated with malaria during pregnancy. Sequestration also removes parasites from the circulation, preventing splenic clearance during one phase of parasite replication and permitting on-going infection.

EPIDEMIOLOGY

Although rarely encountered in the United States, malaria causes approximately 45% of the world's population to be at risk of infection.[2] *P falciparum* and *P vivax* are the most common causes of human malaria and have distinct geographic distributions, as in **Fig. 1**. *P malariae* is found in a similar distribution as *P falciparum*; *P ovale* is primarily found in West Africa, but cases have been reported in other sub-Saharan African countries. The limited cases of *P knowlesi*, a primarily nonhuman primate parasite, are reported in Southeast Asia.

Worldwide over the last 15 years, there has been a 60% decrease in the malaria death rate due to increased availability of preventive measures, such as bed nets, and effective new diagnostics and treatments. Since 2007 when the World Health Organization (WHO) endorsed a global commitment to eradicate malaria, 5 countries have been declared malaria free (United Arab Emirates, Morocco, Turkmenistan, Armenia, and Sri Lanka), and 26 more are poised for elimination by 2020.[3] Despite this progress, in 2015, it is estimated that there were still 214 million new cases of malaria and 438,000 deaths. The vast majority of morbidity and mortality occur in sub-Saharan Africa, where the heaviest burden of disease is shouldered by children less than 5 years of age. Further progress is threatened by the spread of drug and insecticide resistance, the need for new tools for malaria control in areas that have not reduced transmission with current interventions, and the continued demand for a global financial commitment to the goal of eradication.

In the United States, there has been a consistent increase the number of cases of malaria reported to the US Centers for Disease Control and Prevention (CDC) since 1973. In 2013, 1727 cases were reported. All infections in which origin was determined (99.6%) were acquired abroad. Most occurred in US residents, and 17% occurred in children (age <18 years). Severe malaria, infection associated with end organ damage, was more common in children less than 5 year old compared with older children and adults. However, none of the 10 deaths caused by malaria in the United States were among children.[4]

SUSCEPTIBILITY TO INFECTION

In nonendemic and low transmission areas, all individuals are at risk of infection. In highly endemic settings, primarily some areas in sub-Saharan Africa, multiple malaria infections lead to the development of partial immunity. As children in these areas have repeated exposure to malaria infection, they become less likely to experience clinical disease. By adulthood, individuals in high transmission settings may still become infected, but the parasite load is lower and there is very low risk of clinical disease.

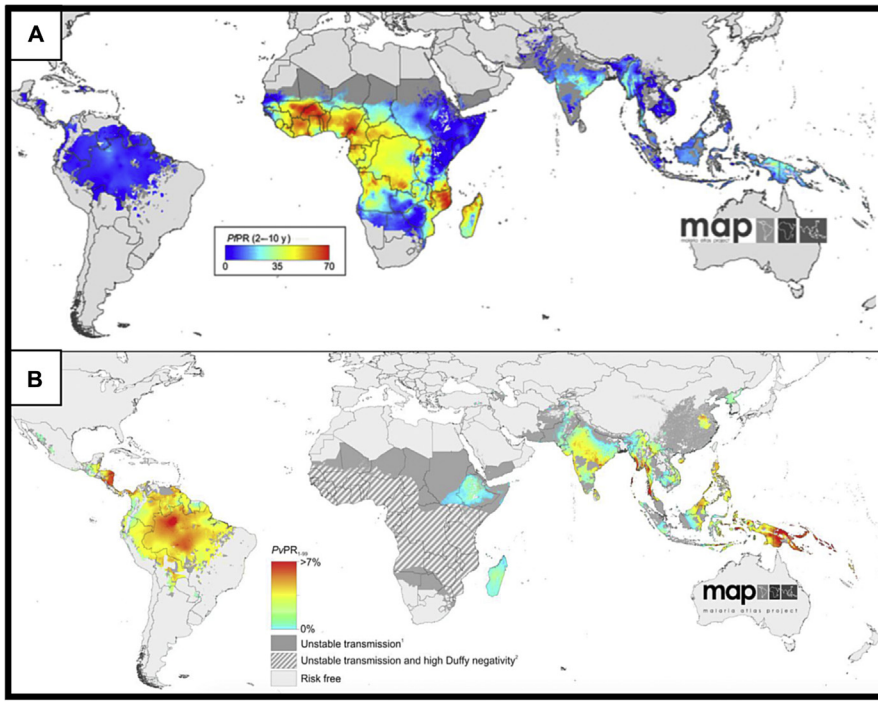

Fig. 1. Spatial distribution of *P falciparum* (*A*) and *P vivax* (*B*) endemicity in 2010. Prevalence rates are presented in different populations and different scales based on species. The *P falciparum* map (*A*) shows the prevalence rate in 2 to 10 year olds (PfPR) and ranges from 0% to 70%; see color scale on map. The *P vivax* map (*B*) shows the prevalence rate in 1 to 99 year olds (PvPR) and ranges from 0 to greater than 7%. Shaded areas have unstable transmission (<0.1%), and hatched areas have greater than 90% prevalence of Duffy antigen negativity. Duffy antigen is required for the invasion of *P vivax* into the erythrocyte and is absent in some African populations. These maps are open source and made available by the Malaria Atlas Project (http://www.map.ox.ac.uk/map/) under the Creative Commons Attribution 3.0 Unported License. (*Reproduced from* [*A*] Gething PW, Patil AP, Smith DL, et al. A new world malaria map: plasmodium falciparum endemicity in 2010. Malar J 2011;10:378; and [*B*] Gething PW, Elyazar IRF, Moyes CL, et al. A long neglected world malaria map: plasmodium vivax endemicity in 2010. PLoS Negl Trop Dis 2012;6(9):e1814.)

Sterilizing immunity, complete prevention of infection, does not occur. Moreover, the duration of acquired immunity is not life-long: if individuals from endemic areas are no longer exposed to infection for as little as a year, they are at risk of disease upon repeat exposure. Many cases of malaria in the United States occur when individuals from endemic countries return home to visit friends and relatives. These individuals may not realize that their immunity has decayed, making them again susceptible to high-density infection and disease.

Hemoglobinopathies alter susceptibility to malaria infection and disease. Sickle cell trait (HbAS) is estimated to afford 90% protection from severe disease, 75% protection from hospitalization with malaria, but no protection from asymptomatic infection.[5,6] This protection contributes to the persistence of HbS in African populations given the decreased life expectancy of homozygotes. Protection is also seen with hemoglobin C and alpha-thalassemia and beta-thalassemia. However, it is important to

recognize that individuals with any of these hemoglobinopathies can still get malaria and have severe manifestations.

HISTORY AND PHYSICAL

During medical evaluation of patients with fever, taking a travel history and considering malaria are critical. Malaria should be suspected in any case of documented or history of fever and residence in or travel to malaria-endemic areas. Key malaria-related questions to ask on history include the following:

- *Has the patient traveled to a malaria-endemic area? Which species are present in that region?* The geographic region determines the possibility of malaria infection and the most likely species, risk of severe disease, and treatment choice based on geographic patterns of antimalarial drug resistance. See the CDC Travelers' Health Web site (http://wwwnc.cdc.gov/travel) for details on malaria epidemiology by country.
- *When did exposure occur?* The time from the bite of an infected mosquito until presentation with clinical illness of *P faliciparum* is typically 10 to 14 days but may be as short as 7 days and as long as 30 days. Presentation with clinical illness may be delayed in those with partial immunity or who were taking incomplete or ineffective prophylaxis. *P malariae* may persist at low levels for long periods of time, up to years. Because of their dormant stages, *P vivax* and *P ovale* may present months to years after initial infections. Three to 6 weeks after the initial infectious bite is the most common period for relapse of *P vivax* infection obtained in tropical areas, and most relapses have occurred by 6 months. Relapse may occur 6 to 12 months after *P vivax* infection obtained in subtropical or temperate climates.[7]
- *Has the patient used antimalarials in the last 1 to 2 months?* Drugs recently used for treatment or prophylaxis should not be used for treatment of clinical illness. Among individuals living in or emigrating from endemic areas, it is important to know if they were treated for malaria in the last 1 to 2 months, what drug was used, and if treatment was completed. Among travelers, it is important to know if they were taking malaria prophylaxis, what drug was used, and what their adherence was. Note that taking prophylaxis, even as recommended, does not definitively exclude malaria diagnosis.

Other groups in which *Plasmodium* infection should be considered in health care include asymptomatic immigrants (refugees, international adoptees, and others) from endemic areas. See the section on "Screening and Treatment of immigrants from malaria endemic areas" in later discussion.

The physical examination and initial laboratory evaluation should be used to determine the likelihood of malaria, evaluate other conditions on the differential, and determine the disease severity if malaria is likely (see **Box 2** and the section, "Assessing severity"). General physical examination should be performed with specific attention to the following organ systems:

- Ophthalmologic: Check for conjunctival pallor indicative of anemia. If seizures, altered consciousness, or other concern for cerebral malaria, consider dilated funduscopic examination by an ophthalmologist to evaluate for retinal hemorrhages, areas of retinal opacification, papilledema, cotton wool spots, or decolorization of retinal vessels.[8]
- Pulmonary: Note tachypnea, which may be related to pulmonary complications (manifested by crepitation) or to metabolic acidosis (manifested by the characteristic acidotic breathing pattern).

- Cardiac: Note tachycardia, which could be related to fever, increased cardiac output demand due to anemia, or shock. Assess capillary refill and extremity temperature variation.
- Gastrointestinal: Palpate for splenomegaly.
- Neurologic: Calculate Glasgow Coma Score if altered mental status and monitor for deterioration. Monitor for seizures. Assess for nuchal rigidity and photophobia, which would suggest meningitis rather than cerebral malaria.

DIFFERENTIAL DIAGNOSIS

Because the symptoms of malaria are nonspecific, the differential diagnosis is broad. Specific alternative diagnoses are listed in **Box 1**.

DIAGNOSIS

Malaria has the potential to be fatal. In cases where the index of suspicion is high, treatment can be started before testing results are available or even before they are performed, so that there is no delay in therapy. If presumptive treatment is initiated, diagnostic specimens should still be obtained.

Blood smear and detection by microscopy are considered the gold standard for laboratory confirmation of malaria. Thick and thin smears should be read. The CDC provides details on preparation and interpretation.[9] Briefly, smears are stained with either Wright's or ideally Giemsa stain. The thick smear is the most sensitive measure to detect low-density infection because it allows the microscopist to review a large volume of blood and is read for detection of infection. The thin smear, which allows greater resolution of the red blood cell morphology and the parasite, is used for determining the *Plasmodium* species and quantifying the specific parasite density. The later features are important for treatment and monitoring decisions. If the initial blood smears are negative but *Plasmodium* infection remains on the differential, 2 additional smears should be obtained at 12- to 24-hour intervals. Blood smears and trends in

Box 1
Differential diagnoses of malaria

Sepsis due to bacteremia
Encephalitis (rickettsial or viral)
Meningitis (bacterial or viral)
Pneumonia (bacterial, viral or fungal)
Typhoid fever
Dengue fever
Chikungunya
Leptospirosis
Brucellosis
Rickettsial infections
Acute schistosomiasis (Katayama fever)
Amebic liver abscess
Acute HIV

parasite quantification are also useful in following response to treatment (see later discussion).

Antigen-detecting rapid diagnostics tests (RDTs) are increasingly available for diagnosis of malaria in both resource-limited and nonendemic settings. The tests are generally cassette- or card-based lateral flow immunochromatographic assays that appear much like a pregnancy test. Labeled antibodies detect 1 of 3 *Plasmodium* antigens that may or may not be species specific depending on the test. Up-to-date information on the tests available, their mechanisms, and performance characteristics can be found on the WHO Foundation for Innovative New Diagnostics Web site.[10]

Only one RDT is approved for use in commercial and hospital laboratories in the United States. The BinaxNOW test (Alere Inc, Waltham, MA, USA) detects one antigen that is specific for *P falciparum* and another that is found in all human *Plasmodium* species. The sensitivity of detecting *P falciparum* and non-*P falciparum* infection in US or Canadian hospitals has ranged from 72% to 100% depending on the study.[11–14] This RDT is specifically less sensitive for the detection of *P malariae* and low-density infections (<200 parasites per microliter). Sensitivity for detection of *P knowlesi* is low (29%).[15] The current recommendations are that RDTs should be used in conjunction with blood smears. RDTs may significantly reduce the time required for preliminary diagnosis and, thus, are useful tools for initial diagnosis.[14] Positive RDTs should be considered significant support of *Plasmodium* infection, but blood smears are required for confirmation, definitive species identification, and quantification. Negative RDTs should not eliminate consideration of malaria, especially if there has been recent treatment or infection is due to low-density or non-*falciparum* infections. Blood smears should be performed to exclude the diagnosis.

All cases of laboratory confirmed malaria should be reported to the state health department and to the CDC (www.cdc.gov/malaria/report.html).

ASSESSMENT OF SEVERITY

Clinical disease is classified as uncomplicated or severe malaria. Uncomplicated malaria is the presence of symptoms and/or signs of malaria and a positive parasitologic test in the absence of evidence of end organ damage. Fever, the quintessential symptom of malaria, is often greater than 40°C and associated with severe rigors and chills and profuse diaphoresis as fever resolves. Although rarely observed, fever is classically periodic with the interval between fevers determined by *Plasmodium* species causing the infection. Fever as well as other common initial symptoms, including malaise, fatigue, headache, cough, abdominal pain, anorexia, nausea, vomiting, diarrhea, myalgias, and back pain, is nonspecific, requiring a high index of suspicion of malaria in anyone with possible exposure. Signs that may be associated with uncomplicated malaria include mild jaundice due to hemolysis and splenic enlargement. Laboratory abnormalities may include mild anemia, thrombocytopenia, mild coagulopathy, increased blood urea nitrogen, and elevated creatinine not meeting criteria for acute kidney injury. Uncomplicated malaria may be caused by any of the *Plasmodium* species infecting humans.

Severe malaria is most often caused by cytoadherence of *P falciparum*–infected erythrocytes in capillary beds of a wide range of organs. The presence of one or more of the features listed in **Box 2** and a positive malaria diagnostic test in the absence of an alternative cause are defined as severe malaria. These manifestations may occur alone or in combination. Specific clinical syndromes that can occur in endemic settings as well as in nonimmune travelers include but are not limited to severe anemia and cerebral malaria. Severe anemia can lead to metabolic acidosis, renal

Box 2
Manifestations of severe malaria adapted from World Health Organization and US Centers for Disease Control and Prevention

- *Impaired consciousness*
- *Prostration:* Generalized weakness leading to inability to sit, stand, or walk without assistance
- *Multiple convulsions:* More than 2 episodes within 24 hours
- *Acidosis:* A base deficit of greater than 8 mEq/L or, if not available, a plasma bicarbonate level of less than 15 mmol/L or venous plasma lactate $\geq$5 mmol/L
- *Hypoglycemia:* Blood or plasma glucose less than 2.2 mmol/L (<40 mg/dL)
- *Severe anemia:* Hemoglobin concentration $\leq$5 g/dL or a hematocrit of $\leq$15% in children less than 12 years of age; less than 7 g/dL, and less than 20%, respectively, in those $\geq$12 year old
- *Renal impairment:* Evidence of acute kidney injury, decreased urine output, decreased glomerular filtration rate, increased creatinine
- *Jaundice:* Plasma or serum bilirubin greater than 50 μmol/L (3 mg/dL) with a parasite count greater than 100,000/μL
- *Pulmonary edema:* Radiologically confirmed or oxygen saturation less than 92% on room air with a respiratory rate greater than 30/min, often with chest indrawing and crepitations on auscultation
- *Significant bleeding:* Including recurrent or prolonged bleeding from the nose, gums, or venipuncture sites; hematemesis or melena
- *Shock:* Compensated shock defined as capillary refill $\geq$3 s or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock defined as systolic blood pressure less than 70 mm Hg with evidence of impaired perfusion (cool peripheries or prolonged capillary refill)
- *Hyperparasitaemia: P falciparum* or *P knowlesi* parasitemia greater than 10% (CDC uses >5% as a cutoff)

Data from US Centers for Disease Control and Prevention. Malaria diagnosis & treatment in the United States. Available at: https://www.cdc.gov/malaria/diagnosis_treatment/index.html. Accessed November 26, 2016; and World Health Organization. Guidelines for the treatment of malaria. 3rd edition. Available at: http://www.who.int/malaria/publications/atoz/9789241549127/en/. Accessed November 26, 2016.

impairment, and noncardiogenic pulmonary edema. Cerebral malaria can present with seizures and/or decreased consciousness, including coma, and can lead to cerebral edema, increased intracranial pressure, herniation, and death.

Laboratory tests and potential findings to use in valuation of potential complications include the following:

- Complete blood count: anemia, thrombocytopenia, leukopenia, or leukocytosis
- Chemistry panel: acidosis, acute kidney injury, and hypoglycemia
- Urinalysis: hemoglobinuria and proteinuria
- Lumbar puncture (if altered consciousness or other indication): findings may be normal or have elevated opening pressure, mildly elevated protein, or mild pleocytosis
- Blood cultures: concomitant bacteremia
- Blood gas: metabolic acidosis with or without respiratory compensation
- Type and cross-match

TREATMENT AND MANAGEMENT

Uncomplicated Malaria

In cases of malaria infection without signs of severe disease, oral treatment should be initiated as promptly as possible (**Table 1**). Hospitalization should be considered for individuals from nonendemic regions, young children, and those with high parasite density (>4%). Choice of antimalarial drug is determined by the species of *Plasmodium* causing the infection, the drug resistance patterns in the region where infection was likely acquired, and whether the patient has taken any other antimalaria drugs in the last 1 to 2 months for treatment or prevention. If the *Plasmodium* species causing the infection is not certain, then the infection should be treated as though it were *P falciparum*. In all areas, drugs that were recently used in the last 1 to 2 months for treatment or prophylaxis should not be used for treatment. Specific dosing recommendations and new updates can be found on the CDC Web site,[16] (also listed in Key Resources).

If *P vivax* or *P ovale* is identified or suspected, primaquine should be administered to prevent relapse due to dormant liver stages. However, primaquine can cause hemolytic anemia and is contraindicated in G6PD-deficient persons. G6PD screening should be done before primaquine treatment. Alternate regimens many be considered in consultation with an infectious disease or tropical medicine expert for persons with borderline or true G6PD-deficiency.

During treatment, parasite density should be monitored daily until negative.[17]

Severe Malaria

When signs or symptoms of severe diseases are present, parenteral treatment should be initiated promptly because death can occur within hours of presentation. Artesunate or quinine/quinidine should be used for treatment. Given the level of monitoring and the frequency of clinical and laboratory assessment required to manage patients with severe malaria, admission to an intensive care unit is recommended. Initial evaluation is described above. Parasite quantification every 12 hours is recommended for the first 2 to 3 days to document response to treatment and to a decrease in parasite quantification. If there is not significant decrease in parasite density by 48 to 72 hours, consider expert consultation.

Supportive care measures, such as fluid resuscitation, cardiac and respiratory monitoring, oxygen, and supportive ventilation, should be provided as clinically indicated. In addition to antimalarial treatment, management of complications may require anticonvulsants, antibiotics, antipyretics, and blood transfusions. Exchange transfusions are no longer recommended.[18,19] Clinical assessments should be repeated every 2 to 4 hours. If there is a decline in mental status after initiation of treatment, clinicians should consider new onset of seizures, hypoglycemia, or worsening anemia. Hypoglycemia is a common complication and may mimic cerebral malaria. Laboratory evaluation, including hemoglobin/hematocrit, glucose, and lactate, should be repeated every 6 hours, and supportive care should be administered based on these results.

Quinidine and artesunate are available in the United States for treatment of severe malaria. Treatment should be initiated with intravenous quinidine if it is available. Quinidine can cause arrhythmias, so intravenous administration of the drug requires close cardiac monitoring.[20] Hypotension is common and should be treated with volume expansion. Baseline electrocardiogram should be performed, and changes in the width of the QRS and length of the QTc should be monitored hourly. The infusion should be held if the QTc prolongs by more than 50% of the baseline length, but

Table 1
General malaria pediatric treatment recommendations and additional information

Syndrome and Species	Drug Resistance in the Region Acquired	Drug Recommendations () = See Notes	Notes
Uncomplicated malaria, *P falciparum* or species unknown	Chloroquine resistant or resistance unknown	A. Atovoquone-proguanil B. Artemether-lumefantrine C. Quinine sulfate plus doxycycline, tetracycline, or (clindamycin) D. Mefloquine	• All areas should be considered chloroquine-resistant unless specifically noted as chloroquine-sensitive below. See CDC Yellow Book for country-specific details • A, B, C equally recommended; due to increased risk of neuropsychiatric complications, D is only recommended if A, B, C are not possible • D. Also not recommended in infections acquired in SE Asia due to resistance • In C, clindamycin is recommended when doxycycline and tetracycline are contraindicated, eg, children <8 y old and pregnant women
	Chloroquine sensitive	Chloroquine phosphate or hydroxychloroquine	• Chloroquine-sensitive areas are Central America west of the Panama canal, Haiti, Dominican Republic, and most of the Middle East • Regimens for chloroquine-resistant infections may be used as available, more convenient, or preferred
Uncomplicated malaria, *P malariae* or *P knowlesi*	All regions	Chloroquine phosphate or hydroxychloroquine	

Uncomplicated malaria, *P ovale* and *P vivax* (chloroquine sensitive)	All regions (except where *P vivax* chloroquine resistance is common, see below)	Chloroquine phosphate plus primaquine or hydroxychloroquine plus primaquine	• See text on use of primaquine • Low rates of chloroquine-resistant *P vivax* have been found in Myanmar, India, Central and South America; chloroquine should be initiated but monitored closely, if no response change to chloroquine-resistant regimen, and report to CDC
Uncomplicated malaria, *P vivax* (chloroquine resistant)	Chloroquine resistant	A. Quinine sulfate plus either doxycycline or tetracycline plus primaquine B. Atovoquone-proguanil plus primaquine C. Mefolquine plus primaquine	• Chloroquine-resistant *P vivax* is well documented in Papua New Guinea and Indonesia
Severe malaria	All regions	Quinidine gluconate plus doxycycline, tetracycline, or clindamycin Investigational new drug (contact CDC): artesunate followed by atovaquone-proguanil, doxycycline, or mefloquine	• Monitor for hypotension, hypoglycemia, and cardiac complications (widening of QRS or lengthening of the QTc interval); see text • Monitor parasite density every 12 h during the first 48–72 h; should decrease 90% in first 48 h • Once parasitemia <1%, may transition to oral regimen: quinine plus oral partner drug OR complete oral course of atovaquone-proguanil or artemether-lumefantrine • Total course for quinidine/quinine based on area of infection origin: 7 d for southeast Asia, 3 d for Africa or South America

Adapted from CDC. Guidelines for the treatment of malaria in the US Centers for Disease Control and Prevention. Malaria diagnosis & treatment in the United States. Available at: https://www.cdc.gov/malaria/diagnosis_treatment/index.html. Accessed November 26, 2016.

may be restarted when the QTc is no more than 25% longer than its original length. Additional side effects and toxicities include hypoglycemia, tinnitus, reversible hearing loss, dizziness, vision changes, nausea, and vomiting.

Artesunate is available as an investigational new drug through the CDC. Criteria for access to artesunate are confirmed cases of malaria requiring parenteral therapy because of severe malaria, parasitemia greater than 5%, or inability to tolerate oral therapy. In addition, one of the following must be true: artesunate is more readily available than quinidine; quinidine is contraindicated; or there was intolerance to or failure of quinidine.[21] A retrospective case series of participants in this experimental protocol showed that artesunate is safe and clinically beneficial.[22] Clinical trials in endemic settings and a systematic review show significantly lower rates of mortality using artesunate compared with quinine.[23–25] The CDC Malaria Hotline (contact information in "When to Refer" section) should be called for access to and use of artesunate.

After parenteral therapy for at least 24 hours, parasite density is less than 1%, and the patient can tolerate oral medications, treatment may be transitioned to an oral regimen (see **Table 1**). Complete courses of atovaquone-proguanil or lumefantrine-artemether may be used and may be preferred given they are better tolerated than oral quinine.

WHEN TO REFER

All suspected malaria cases should be seen in consultation with an infectious disease expert. Cases with any manifestations of severe disease may require management in an intensive care setting. The CDC staffs a malaria hotline and can provide additional consultation (Monday-Friday 9 AM to 5 PM EST, call either (770) 488-7788 or (855) 856-4713; after hours, weekends, and holidays call (770) 488-7100 and ask for the malaria clinician on call).

SCREENING AND TREATMENT OF IMMIGRANTS FROM MALARIA-ENDEMIC AREAS

In medical evaluations of asymptomatic immigrants (refugees, international adoptees, and others) from endemic areas, any history of malaria infection and treatment should be noted and signs of chronic infection evaluated, such as anemia and splenomegaly. If these signs of chronic infection are detected, then malaria diagnostic tests should be performed and any detected infections should be treated with oral medication, as described above.

In the absence of evidence of acute or chronic infection, the CDC provides guidelines for the treatment of these populations, which are summarized here.[26] More details may be found on the Web site listed in **Box 3**.

Box 3
Key guidelines and sources for malaria diagnosis and treatment

World Health Organization
Diagnosis and treatment guidelines: http://www.who.int/malaria/areas/treatment/en/

US Centers for Disease Control and Prevention
General information: https://www.cdc.gov/malaria/
Diagnosis and treatment guidelines: https://www.cdc.gov/malaria/diagnosis_treatment/index.html
Prophylaxis: http://wwwnc.cdc.gov/travel/yellowbook/2016/table-of-contents
Immigrant and refugee health: http://www.cdc.gov/immigrantrefugeehealth/guidelines/domestic/malaria-guidelines-domestic.html

Refugees from malaria-endemic areas in sub-Saharan Africa without evidence of acute or chronic infection: Refugees should have received presumptive malaria treatment before departure for the United States. If documentation of predeparture treatment is not available, then postarrival presumptive treatment should be considered. Children weighing less than 5 kg and pregnant women may have been screened for

Table 2
Drugs for malaria prophylaxis currently available in the United States

	Pros	Cons	Regimen
Atovaquone-proguanil	• Minimal side effects • Good for short trips given short posttravel duration of treatment	• Contraindicated in pregnancy, children <5 kg, severe renal impairment • Increases effect of warfarin • More expensive than other options	Pretravel: 1–2 d During travel: Daily Posttravel: 7 d
Doxycycline	• Inexpensive • Readily available • May prevent other infections as well, eg, rickettsial infections and leptospirosis	• Photosensitivity • Risk of *Candida* vaginitis • Esophagitis and gastrointestinal side effects: Take with meal or sufficient fluids, do not take just before bed • Contraindicated in pregnancy and children <8 y old	Pretravel: 1–2 d During travel: Daily Posttravel: 4 wk
Mefloquine	• Recommended choice for pregnant women traveling to areas with chloroquine resistance	• Rare but serious neuropsychiatric side effects • Contraindicated in people with some psychiatric conditions, seizure disorders, and cardiac conduction abnormalities	Pretravel: $\geq$2 wk During travel: Weekly Posttravel: 4 wk
Chloroquine	• Minimal side effects • Safe in pregnancy	• Limited geographic range (Central America west of the Panama canal, Haiti, Dominican Republic, and most of the Middle East)	Pretravel: 1–2 wk During travel: Weekly Posttravel: 4 wk
Primaquine	• Most effective choice for short trips to areas where >90% of infection is caused by *P vivax*	• G6PD testing required • Contraindicated in people with G6PD-deficiency and pregnancy	Primary prophylaxis Pretravel: 1–2 d During travel: Daily Posttravel: 7 d Terminal prophylaxis following use of other regimen for primary prevention Posttravel: 14 d

infection and only treated if positive. Presumptive treatment or screening and treatment are not recommended for refugees from other areas.

International adoptees without evidence of acute or chronic infection: In contrast to refugees, guidelines for international adoptees do not recommend presumptive treatment or screening. However, a recent study of asymptomatic *Plasmodium* infection in international adoptees from Ethiopia found 14% had infection, leading the investigators to suggest that screening with polymerase chain reaction be recommended.[27]

PROPHYLAXIS

Prophylaxis against malaria is recommended for all travelers to malaria-endemic areas. Specific recommendations are updated every 2 years and can be found in the CDC Yellow Book (see link in **Box 3**). The 5 drugs currently available in the United States for malaria prophylaxis are listed in **Table 2**. Choice of drug is determined primarily by the species distribution and drug-resistance patterns in the destination and patient characteristics.

SUMMARY

- Globally, there has been a significant decrease in *Plasmodium* infection and reduction of malaria-related morbidity and mortality in the last 15 years.
- The number of cases of malaria imported to the United States continues to increase likely due to increased global travel.
- Prompt provision of effective treatment is critical to limiting the complications of malaria.
- Understanding *Plasmodium* species variation and the epidemiology and drug resistance patterns in the geographic area where infection was acquired is important for determining the most appropriate treatment regimens.
- Easy-to-use and up-to-date guidelines for the treatment and management of malaria in endemic areas and in the United States are accessible online from key reference organizations.

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