Treatment of Malaria in the United States
A Systematic Review

Kevin S. Griffith, MD, MPH
Linda S. Lewis, DVM, MPVM
Sonja Mali, MPH
Monica E. Parise, MD

EVEN THOUGH ENDEMIC MALARIA has been eliminated from the United States, it remains a leading infectious disease worldwide. As a consequence, every year in the United States an average 1200 cases of malaria are reported, almost all imported, resulting in up to 13 deaths per year.1 The unfamiliarity of US clinicians and laboratory personnel with malaria and drug resistance patterns has contributed to delays in diagnosis and treatment, at times with adverse outcomes.2

To address this problem, we provide clinicians with practical recommendations for the diagnosis and treatment of malaria in the United States, based on published evidence; the Centers for Disease Control and Prevention (CDC) experience in assisting US clinicians; and the available drugs and diagnostic modalities used in this country.

METHODS

We performed a systematic MEDLINE search from 1966 to 2006 using the search term malaria (with the subheadings congenital, diagnosis, drug therapy, epidemiology, and therapy). This search was conducted on August 1, 2006, and resulted in 5588 potentially relevant articles. We reviewed titles and/or abstracts of all articles to determine relevance to this article, hand searched bibliographies of pertinent articles, and reviewed articles suggested by experts in the treatment of malaria in North America. Recommendations are based on randomized controlled trials, observational studies, and consensus expert opinion.

Context Many US clinicians and laboratory personnel are unfamiliar with the diagnosis and treatment of malaria.

Objectives To examine the evidence base for management of uncomplicated and severe malaria and to provide clinicians with practical recommendations for the diagnosis and treatment of malaria in the United States.

Evidence Acquisition Systematic MEDLINE search from 1966 to 2006 using the search term malaria (with the subheadings congenital, diagnosis, drug therapy, epidemiology, and therapy). Additional references were obtained from searching the bibliographies of pertinent articles and by reviewing articles suggested by experts in the treatment of malaria in North America.

Evidence Synthesis Important measures to reduce morbidity and mortality from malaria in the United States include the following: obtaining a travel history, considering malaria in the differential diagnosis of fever based on the travel history, and prompt and accurate diagnosis and treatment. Chloroquine remains the treatment of choice for Plasmodium falciparum acquired in areas without chloroquine-resistant strains. In areas with chloroquine resistance, a combination of atovaquone and proguanil or quinine plus tetracycline or doxycycline or clindamycin are the best treatment options. Chloroquine remains the treatment of choice for all other malaria species, with the exception of P vivax acquired in Indonesia or Papua New Guinea, in which case atovaquone-proguanil is best, with mefloquine or quinine plus tetracycline or doxycycline as alternatives. Quinidine is currently the recommended treatment for severe malaria in the United States because the artemisinins are not yet available. Severe malaria occurs when a patient with asexual malaria parasitemia, and no other confirmed cause of symptoms, has 1 or more designated clinical or laboratory findings. The only adjunctive measure recommended in severe malaria is exchange transfusion.

Conclusions Malaria remains a diagnostic and treatment challenge for US clinicians as increasing numbers of persons travel to and emigrate from malarious areas. A strong evidence base exists to help clinicians rapidly initiate appropriate therapy and minimize the major mortality and morbidity burdens caused by this disease.

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Author Affiliations: Malaria Branch, Division of Parasitic Diseases, National Center for Zoonotic, Vector-Borne and Enteric Diseases, Centers for Disease Control and Prevention. Corresponding Author: Monica E. Parise, MD, Parasitic Diseases Branch, Division of Parasitic Diseases, National Center for Zoonotic, Vector-Borne and Enteric Diseases, Centers for Disease Control and Prevention, 4770 Buford Hwy NE MS F22, Atlanta, GA 30341 (MParise@cdc.gov).

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BIOLOGICAL AND EPIDEMIOLOGIC CONSIDERATIONS

In the Plasmodium life cycle (FIGURE 1), the asexual blood stages (rings, trophozoites, schizonts) are responsible for the symptoms of malaria, and thus are the main target of chemotherapy. The sexual blood stages (gametocytes) do not cause any known pathology and thus are not a primary target of treatment. Dormant liver stage parasites (hypnozoites) of Plasmodium vivax and Plasmodium ovale may reactivate weeks or months after the initial infection, producing relapses.

Of the 4 Plasmodium species that infect humans, Plasmodium falciparum is the one with potential to rapidly progress to severe illness or death. It predominates in sub-Saharan Africa, Hispaniola, and Papua New Guinea. Among the other species, P vivax is the most common and predominates in South Asia, Eastern Europe and Northern Asia, and Central and most of South America. Plasmodium ovale occurs mostly in West Africa and is occasionally encountered in Southeast Asia and Papua New Guinea. Plasmodium malariae occurs at low frequency in a patchy distribution worldwide. Plasmodium falciparum accounts for slightly more than 50% and P vivax approximately 25% of reported cases in the United States. Chloroquine-resistant strains of P falciparum occur in all endemic areas except Central America west of the Panama Canal, Mexico, Hispaniola, and parts of

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China and the Middle East, and multidrug-resistant strains occur in Southeast Asia, South America, and sub-Saharan Africa. Due to increasing resistance of *P falciparum* to the drug combination of sulfadoxine and pyrimethamine, the CDC no longer recommends sulfadoxine-pyrimethamine for treatment of malaria in the United States or as standby treatment for US travelers. A high prevalence of chloroquine-resistant *P vivax* (CRPV) is found in Papua New Guinea and Indonesia. Baird and Hoffman have written an excellent review on CRPV (which details well its geographic distribution). There is evidence for rates up to 25% in a few sites in Burma, Malaysia, Vietnam, India, and Turkey.

**RECOGNITION AND DIAGNOSIS**

Consideration of malaria based on travel history is the key to diagnosis. Any patient who has been in an endemic area in the year preceding the onset of malarial symptoms should be evaluated for the disease. The typical incubation period usually varies between 9 and 18 days for *P falciparum*, *P vivax*, and *P ovale,* but it is longer (18-40 days) for *P malariae* and may be as short as 7 days for *P falciparum.* However, symptoms may occur weeks or even months after exposure as a result of inadequate prophylaxis or treatment, immune response, or relapses. Some temperate strains of *P vivax*, such as the North Indian and North Korean strains, can exhibit delayed primary attacks, occurring 12 to 18 months after an infected mosquito bite. Of cases reported in the United States from 1995 to 2004, 98% (n = 3626) of patients with *P falciparum* malaria experienced their first symptoms within the first 3 months of arrival in the United States, and 57% (n = 1743) and 96% (n = 2906) of patients with non-falciparum malaria had symptom onset within the first 3 and 12 months, respectively. During this same time period, 85% of patients with imported *P falciparum* malaria acquired their infection in Africa.

Absence of a travel history does not rule out malaria. Patients may provide an inaccurate history or may have been infected in the United States through other rarely occurring mechanisms such as transfusion, congenital transmission, or local mosquito-borne transmission.

The initial presentation of malaria is nonspecific and similar to that of many other febrile illnesses. Fever is the most commonly reported symptom, being present in 78% to 100% of case patients, but fever periodicity is often not seen. Patients may experience a wide spectrum of other symptoms including chills, headache, malaise, nausea, vomiting, diarrhea, abdominal pain, myalgias, back pain, weakness, dizziness, confusion, cough, and/or coma. Splenomegaly is a frequent physical finding (24%-40% of case patients). Severe malaria is characterized by 1 or more of the signs or symptoms shown in the BOX. Severe malaria is almost invariably caused by *P falciparum*, with rare reports of severe malaria caused by *P vivax*.

Diagnostic confirmation is obtained by microscopic demonstration of malaria parasites on Giemsa-stained thick and thin blood films, which should be examined as soon as possible but within 12 hours of the presentation of any patient with suspected malaria. Institutions unfamiliar with malaria diagnosis should not delay microscopic diagnosis (eg, by sending the films out to a laboratory that cannot provide same-day results), but should promptly refer the patient to a more experienced institution or consult with more experienced personnel at other institutions, their state department of health, or submit digital images captured from stained films directly to the CDC’s telediagnostic service (dpdx@cdc.gov, or through the CDC Malaria Hotline or CDC Emergency Operations Center [Malaria Hotline 770-488-7788 Monday-Friday, 8 AM to 4:30 PM. Off-hours, weekends, and federal holidays, CDC clinicians can be reached by calling the CDC Emergency Operations Center at 770-488-7100 and asking for the malaria clinician on-call to be paged]).

The parasite density (ie, percentage of infected erythrocytes on a thin film) should be quantified as 1 measure of the severity of the disease and its response to treatment, which should be closely monitored. If the initial film is negative and the patient is suspected of having malaria, blood films should be repeated at 12- to 24-hour intervals for 48 to 72 hours. If the diagnosis is clinically suspected and proficient laboratory diagnosis is impossible, empirical treatment for *P falciparum* malaria, as discussed below, should be initiated, pending referral of the patient and/or specimen. It is important that a differential identification of Babesia sp (which may be morphologically similar to *P falciparum*) be made during microscopic examination. Although nonspecific, thrombocytopenia, a low white blood cell count, and signs of hemolysis, such as an elevated bilirubin level, found during general laboratory testing are possible clues to the presence of malaria.
In addition to microscopy, polymerase chain reaction and rapid immunochromatographic diagnostic tests are alternate diagnostic tools that are not routinely available. Rapid immunochromatographic diagnostic tests are not yet licensed for use in the United States. Serological tests document past exposure and are thus of limited use in acute case management.

**CLINICAL SITUATIONS AND RECOMMENDED TREATMENT General**

To manage malaria successfully, treating physicians should seek the answer to the following 5 questions: (1) What is the species? (2) What is the density of parasitemia? (3) What is the drug-resistant pattern where the infection was acquired? (4) Are there signs of severe malaria? and (5) Can the patient tolerate oral medication?

Patients with malaria should be treated immediately because *P falciparum* infections can rapidly progress to severe illness or death in as little as 1 to 2 days. Immunity wanes in the absence of continued antigen exposure and thus semi-immune persons who have left an endemic area for an extended period of time and then return are susceptible to severe disease and death. If the species cannot be identified, the patient should be treated as if infected with *P falciparum* until the infecting species can be identified. The patient’s travel history provides useful clues for selecting an effective antimalarial drug, in terms of risk of drug resistance. Because base and salt conversions for antimalarial drugs are a source of confusion and can result in treatment errors, where pertinent, the base equivalency is followed by the salt equivalency in parentheses (Table).

There has been some controversy about the need for initial hospital admission for all patients with *P falciparum* malaria, and some authors have tried to define triage criteria for which patients need to be admitted vs those who can be followed as outpatients. However, since these patients can deteriorate rapidly and progress to death within 1 to 2 days, and many centers do not have the expertise to adequately triage (eg, to accurately quantify the parasite density), the CDC advises that patients infected with *P falciparum* or an unidentified Plasmodium species should be initially admitted to ensure that the medication is tolerated and the patient is improving clinically and parasitologically. Blood films should be repeated to ensure clearance of *P falciparum* parasitemia. Patients who are not responding clinically (with defervescence within 72 hours) need follow-up malaria blood films and may also require a search for other causes of fever. Of note, gametocytes may be less susceptible to many antimalarial drugs than are asexual parasites, and their persistence in the blood in the absence of asexual parasites does not indicate drug resistance.

**Uncomplicated Falciparum Malaria**

For *P falciparum* malaria acquired in a limited number of areas (Figure 2), chloroquine (with hydroxychloroquine as a second-line alternative) remains the treatment of choice (Table). Chloroquine-resistant *P falciparum* strains are found in all other malaria areas, where 3 treatment options are currently recommended: (1) oral quinine plus either tetracycline, doxycycline, or clindamycin; (2) atovaquone-proguanil; or (3) mefloquine. The first 2 options are preferred due to a higher rate of moderate to severe neuropsychiatric reactions seen when mefloquine is used at treatment doses compared with persons taking the drug for prophylaxis. The incidence rate for moderate or severe neuropsychiatric adverse reactions at mefloquine treatment doses has been estimated to be 1 in 215 to 1 in 1754 treatments. None of the reported neuropsychiatric adverse reactions were lethal and most resolved spontaneously. Atovaquone-proguanil was better tolerated than the combination of quinine and tetracycline in one trial that directly compared the 2 regimens.

Quinine has a rapid onset of action and, in combination with either tetracycline, doxycycline, or clindamycin, has been shown to be a very efficacious treatment option for *P falciparum* infections acquired in regions with chloroquine-resistant strains. For *P falciparum* infections acquired in Southeast Asia, a 7-day course of both quinine and the accompanying antibiotic is recommended, for infections acquired outside Southeast Asia, a 3-day course of quinine and a 7-day course of the accompanying antibiotic is recommended. The quinine and antibiotic should be started at the same time or should at least overlap by 2 days. Although published treatment trials mainly used quinione in combination with tetracycline, doxycycline has excellent antimalarial efficacy in chemoprophylaxis trials and is considered an equally efficacious substitute. Tetracycline or doxycycline is generally preferred to clindamycin as the accompanying antibiotic because of more extensive efficacy data and field experience. The quinine and clindamycin regimen also has been shown to be efficacious against *P falciparum* infections acquired in areas with chloroquine resistance and is useful in treatment of pregnant women and children younger than 8 years in whom tetracyclines and doxycycline are contraindicated.

Quinine is commercially available in the United States only as an oral medication. Cinchonism (a complex of symptoms including nausea, vomiting, headache, tinnitus, deafness, dizziness, and visual disturbances) is common with quinine or quinidine (the isomer of quinine) use. For example, tinnitus was reported in 13% to 94% of patients taking quinine in clinical trials, and the syndrome of cinchonism was reported in 94% of patients in another trial. Quinine binding to plasma proteins, principally to α1-glycoprotein, is increased in malaria. This explains why plasma quinine levels that have been
Table. Antimalarial Drugs Available in the United States Recommended for Use in the Treatment of Malaria

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<tr>
<th>Drug</th>
<th>Indication</th>
<th>Adult Dosage</th>
<th>Pediatric Dosagea</th>
<th>Potential Adverse Effects</th>
<th>Comments</th>
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<tr>
<td>Atovaquone-proguanil</td>
<td>Plasmodium falciparum from</td>
<td>Adult tablet = 250 mg atovaquone/100 mg proguanil</td>
<td>Pediatric tablet = 62.5 mg atovaquone/25 mg proguanil</td>
<td>Abdominal pain, 5-8 kg: 2 pediatric tablets orally per day × 3 d 8-10 kg: 3 pediatric tablets orally per day × 3 d 10-20 kg: 1 adult tablet orally per day × 3 d 20-30 kg: 2 adult tablets orally per day × 3 d 30-40 kg: 3 adult tablets orally per day × 3 d 40 kg: 4 adult tablets orally per day × 3 d</td>
<td>Not indicated for use in pregnant women due to limited data Contraindicated if hypersensitivity to atovaquone or proguanil; severe renal impairment (creatinine clearance &lt;30 mL/min) Should be taken with food to increase absorption of atovaquone</td>
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<td>chloroquine-resistant areas</td>
<td>4 Adult tablets orally per day × 3 d</td>
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<td>Chloroquine phosphates</td>
<td></td>
<td>600-mg base (= 1000 mg salt) orally immediately, followed by 300-mg base (= 500 mg salt) orally at 6, 24, and 48 h Total dose: 1500-mg base (= 2500 mg salt)</td>
<td>10-mg base/kg orally immediately, followed by 5-mg base/kg orally at 6, 24, and 48 h Total dose: 25-mg base/kg</td>
<td>Nausea, vomiting, diarrhea, rash, abdominal pain, pruritus</td>
<td>Safe in children and pregnant women Give for chemoprophylaxis (500 mg salt orally every 3 days in pregnant women with chloroquine-sensitive P falciparum) Contraindicated if retinal or visual field change; hypersensitivity to 4-aminoquinolines Use with caution in those with impaired liver function since the drug is concentrated in the liver</td>
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<td>Oral: 20-mg base/kg/d orally divided 3 times daily IV: 10-mg base/kg loading dose IV followed by 5-mg base/kg IV every 8 h; switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication; treatment course = 7 d</td>
<td>Oral: 20-mg base/kg/d orally divided 3 times daily × 7 d IV: 10-mg base/kg loading dose IV followed by 5-mg base/kg IV every 8 h; switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication; treatment course = 7 d</td>
<td>Diarrhea, nausea, rash</td>
<td>Always use in combination with quinine-quinidine Safe in children and pregnant women</td>
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<td>Clindamycin</td>
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<td>Oral: 100 mg orally twice daily × 7 d IV: 100 mg IV every 12 h and then switch to oral doxycycline (as above) as soon as patient can take oral medication; treatment course = 7 d</td>
<td>Oral: 2.2 mg/kg orally every 12 h × 7 d IV: IV only if patient is not able to take oral medication; for children &lt;45 kg, give 2.2 mg/kg IV every 12 h and then switch to oral doxycycline (dose as above) as soon as patient can take oral medication; for children ≥45 kg, use same dosing as for adults; treatment course = 7 d</td>
<td>Nausea, vomiting, diarrhea, abdominal pain, dizziness, photosensitivity, headache, esophagitis, odynophagia, rarely hepatotoxicity, pancreatitis, and benign intracranial hypertension seen with tetracycline class of drugs</td>
<td>Always use in combination with quinine-quinidine Contraindicated in children &lt;8 y; pregnant women, and persons with known hypersensitivity to tetracyclines While food, milk, and divalent and trivalent cations decrease the absorption of tetracycline, doxycycline can be taken with food, including milk products, which helps to decrease gastrointestinal disturbances To prevent esophagitis, the tetracyclines should be taken with large amounts of fluids, and patients should not lie down for 1 h after taking the drugs Concurrent treatment with barbiturates, carbamazepine, or phenytoin may cause a reduction in serum concentrations of doxycycline</td>
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<td>Doxycycline</td>
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<td>620-mg base (= 800 mg salt) orally immediately, followed by 310-mg base (= 400 mg salt) orally at 6, 24, and 48 h Total dose: 1550-mg base (= 2000 mg salt)</td>
<td>10-mg base/kg orally immediately, followed by 5-mg base/kg orally at 6, 24, and 48 h Total dose: 25-mg base/kg</td>
<td>Nausea, vomiting, rash, headache, dizziness, uticaria, abdominal pain, pruritus</td>
<td>Safe in children and pregnant women Give for chemoprophylaxis (310-mg base orally every week) in pregnant women with chloroquine-sensitive P falciparum Contraindicated if retinal or visual field change; hypersensitivity to 4-aminoquinolines Use with caution in those with impaired liver function</td>
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<th>Comments</th>
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<tbody>
<tr>
<td>Mefloquine</td>
<td>P. falciparum from chloroquine-resistant areas, except Thailand-Burmees and Cambodian border regions</td>
<td>684-mg base (= 750 mg salt) orally as initial dose, followed by 456-mg base (= 500 mg salt) orally given 6-12 h after initial dose</td>
<td>Total dose = 1250 mg salt</td>
<td>Gastrointestinal complaints (nausea, vomiting, diarrhea, abdominal pain),</td>
<td>Contraindicated if hypersensitive to the drug or to related compounds; cardiac conduction abnormalities; psychiatric disorders; and seizure disorders. Do not administer if patient has received related drugs (chloroquine, quinine, quinidine) less than 12 h ago. May be used for chemoprophylaxis (250 mg salt orally every week) in pregnant women with chloroquine-resistant P. vivax.</td>
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<td>Primaquine phosphate</td>
<td>Radical cure of P. vivax and P. ovale (to eliminate hypnozoites)</td>
<td>30-mg base orally per day × 14 d</td>
<td>0.5-mg base/kg orally per day × 14 d</td>
<td>Gastrointestinal disturbances, methemoglobinemia (self-limited), hemolysis in persons with G6PD deficiency. Must screen for G6PD deficiency prior to use. Contraindicated in pregnant women. Should be taken with food to minimize gastrointestinal adverse effects.</td>
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<tr>
<td>Quinine sulfate</td>
<td>P. falciparum from chloroquine-resistant areas, except Thailand-Burmees and Cambodian border regions</td>
<td>542-mg base (= 650 mg salt) orally as initial dose, followed by 363-mg base (= 400 mg salt) orally given 6-12 h after initial dose</td>
<td>Total dose = 834 mg salt / Total dose = 834 mg salt</td>
<td>Cinchonism, arrhythmias, atioventricular block, prolongation QT interval, ventricular tachycardia, ventricular fibrillation (these are rare and more commonly seen with quinine), hypoglycemia.</td>
<td>Combine with tetracycline, doxycycline, or clindamycin, except for P. vivax infections in children &lt;8 y or pregnant women. Contraindicated in hypersensitivity including history of blackwater fever, thrombocytopenic purpura, or thrombocytopenia associated with quinine or quinidine use; many cardiac conduction defects and arrhythmias, myasthenia gravis, optic neuritis.</td>
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<tr>
<td>Quinidine gluconate</td>
<td>Severe malaria (all species, independently of chloroquine resistance)</td>
<td>6.25-mg base/kg (= 10 mg salt/kg) loading dose IV over 1-2 h, then 0.0125-mg base/kg/min (= 0.02 mg salt/kg/min) continuous infusion for at least 24 h</td>
<td>Same as adult dose</td>
<td>Cinchonism, tachycardia, prolongation QT intervals, flattening T-wave (effects are often transient), Ventricular arrhythmias, hypotension, hypoglycemia.</td>
<td>Combine with tetracycline, doxycycline, or clindamycin. Contraindicated in hypersensitivity; history of blackwater fever including history of blackwater fever, thrombocytopenic purpura or thrombocytopenia associated with quinine or quinidine use; many cardiac conduction defects and arrhythmias, myasthenia gravis, optic neuritis.</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>P. falciparum from chloroquine-resistant areas, except Thailand-Burmees and Cambodian border regions</td>
<td>Oral: 250 mg orally 4 times daily × 7 d IV: dosage same as for oral</td>
<td>25 mg/kg/d orally divided 4 times daily × 7 d IV: dosage same as for oral</td>
<td>See doxycycline</td>
<td>See doxycycline</td>
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</table>
**Figure 2. Malaria Treatment Algorithm**

**History of Travel to Malaria-Endemic Area or Clinical Suspicion of Malaria**

Perform Thick and Thin Blood Films and Read in <12 h

**Blood Film Positive?**

- No
  - Repeat Blood Films Every 12 to 24 h for 48 to 72 h
  - No
    - Blood Film Positive? (Uncomplicated Malaria)
      - Determine Infecting Species Using Blood Film
        - **Plasmodium falciparum or Species Not Yet Identified**
          - Acquired in Chloroquine-Sensitive Area
            - Chloroquine (Second-Line Treatment: Hydroxychloroquine)
            - Primaquine If Not G6PD Deficient
              - If G6PD Deficient, Counsel About Possibility of Recurrence
            - Repeat Blood Films If Symptoms Recur
          - Acquired in Chloroquine-Resistant Area
            - Atovaquone-Proguanil Alternatives: Quinine Plus Tetracycline, or Doxycycline, or Mefloquine
            - Oral Quinine Plus Tetracycline, or Doxycycline, or Clindamycin or Atovaquone-Proguanil or Mefloquine If Above Not Available
            - Primaquine If Not G6PD Deficient
              - If G6PD Deficient, Counsel About Possibility of Recurrence
            - Repeat Blood Films If Symptoms Recur
          - Intravenous Quinidine Plus Tetracycline, or Doxycycline, or Clindamycin
            - Admit to Intensive Care Unit
            - Monitor Cardiac Function Continuously and Monitor Blood Pressure Frequently
            - Monitor Parasitemia, Glucose, Hemoglobin, and Electrolytes Periodically
            - Prevent and Treat Complications
            - Consider Exchange Transfusion If Parasite Density >10% or If Patient Has Altered Mental Status, Nonvolume Overload Pulmonary Edema, or Renal Complications
            - Switch to Oral Antimalarial Medication When Possible
          - **Plasmodium malariae**
            - Chloroquine (Second-Line Treatment: Hydroxychloroquine)
            - Primarque If Not G6PD Deficient
              - If G6PD Deficient, Counsel About Possibility of Recurrence
            - Repeat Blood Films If Symptoms Recur
          - **Plasmodium ovale or Plasmodium vivax**
            - Chloroquine (Second-Line Treatment: Hydroxychloroquine)
            - Primarque If Not G6PD Deficient
              - If G6PD Deficient, Counsel About Possibility of Recurrence
            - Repeat Blood Films If Symptoms Recur
          - **P. vivax Acquired in Papua New Guinea or Indonesia**
            - Atovaquone-Proguanil Alternatives: Quinine Plus Tetracycline, or Doxycycline, or Mefloquine
            - Oral Quinine Plus Tetracycline, or Doxycycline, or Clindamycin or Atovaquone-Proguanil or Mefloquine If Above Not Available
            - Primarque If Not G6PD Deficient
              - If G6PD Deficient, Counsel About Possibility of Recurrence
            - Repeat Blood Films If Symptoms Recur
          - **Acquired in Chloroquine-Sensitive Area**
            - Chloroquine (Second-Line Treatment: Hydroxychloroquine)
            - Primarque If Not G6PD Deficient
              - If G6PD Deficient, Counsel About Possibility of Recurrence
            - Repeat Blood Films If Symptoms Recur
          - **Acquired in Chloroquine-Resistant Area**
            - Atovaquone-Proguanil Alternatives: Quinine Plus Tetracycline, or Doxycycline, or Mefloquine
            - Oral Quinine Plus Tetracycline, or Doxycycline, or Clindamycin or Atovaquone-Proguanil or Mefloquine If Above Not Available
            - Primarque If Not G6PD Deficient
              - If G6PD Deficient, Counsel About Possibility of Recurrence
            - Repeat Blood Films If Symptoms Recur
          - **Non-Falciparum Species**
            - Chloroquine (Second-Line Treatment: Hydroxychloroquine)
            - Primarque If Not G6PD Deficient
              - If G6PD Deficient, Counsel About Possibility of Recurrence
            - Repeat Blood Films If Symptoms Recur
          - **Plasmodium falciparum**
            - Chloroquine (Second-Line Treatment: Hydroxychloroquine)
            - Primarque If Not G6PD Deficient
              - If G6PD Deficient, Counsel About Possibility of Recurrence
            - Repeat Blood Films If Symptoms Recur

**Blood Film Positive?**

- Yes
  - Calculate Parasite Density
  - Evaluate Clinical Status and Disease Severity
  - Consider Alternate Diagnosis

Severe Malaria and/or Patient Unable to Take Oral Medication

Regardless of Infecting Species or Geographic Region of Acquisition

*If species not yet identified is subsequently diagnosed as a non-falciparum infection, then complete treatment as per the identified species recommendations. G6PD indicates glucose-6-phosphate dehydrogenase. †Central America west of the Panama Canal, Mexico, Hispaniola, parts of China, and the Middle East. ‡All malaria-endemic countries except those listed in second footnote. §Contraindicated in pregnant women and children younger than 8 years of age. |Drug options for chloroquine-resistant *P falciparum* may also be used if chloroquine or hydroxychloroquine cannot be used.
associated with blindness and deafness after self-poisoning, and which are common during the treatment of malaria, extremely rarely cause such adverse effects in patients with malaria.\textsuperscript{91,92} Life-threatening toxicity is rare and the symptoms of cinchonism are rarely sufficient to warrant discontinuing quinine or quinidine treatment.\textsuperscript{93}

The tetracyclines (tetracycline and doxycycline) and clindamycin should always be used in combination with a faster-acting antimalarial drug such as quinine and never as monotherapy.

Atovaquone-proguanil has reported cure rates of 94\% to 100\% for \textit{P falciparum} infections acquired in Southeast Asia, Africa, and South America.\textsuperscript{52,94-100} To date, there have been 12 published cases of atovaquone-proguanil failure for the treatment of \textit{P falciparum} malaria (from East, West, and Central Africa), 7 of which have had isolates with genetically confirmed markers of resistance (ie, mutations in the cytochrome \textit{b} gene),\textsuperscript{110-117} and thus, clinicians should remain aware of the rare possibility of atovaquone-proguanil treatment failures.

Mefloquine should not be used to treat \textit{P falciparum} infections acquired on the borders of Thailand with Burma (Myanmar) and Cambodia, in the western provinces of Cambodia, in the eastern states of Burma (Myanmar), on the border between Burma and China, in Laos along the borders of Laos and Burma, and in the adjacent parts of the Thailand Cambodia border, as well as in southern Vietnam, because of reports of a high prevalence of mefloquine-resistant \textit{P falciparum} in these areas.\textsuperscript{118}

Although mefloquine is contraindicated for chemoprophylactic use in persons with active or recent history of depression, generalized anxiety disorder, psychosis, or other major psychiatric disorder, or in persons with a history of seizures, it can be used for treatment in persons with these conditions if the benefits are judged to outweigh the risks.\textsuperscript{119} If related compounds (chloroquine, quinine, or quinidine) have been given for chemoprophylaxis or initial treatment, mefloquine administration should be delayed at least 12 hours after the last dose of the related compound to minimize the risk of adverse events such as electrocardiographic abnormalities.\textsuperscript{119,120}

Antimalarial drugs that are not recommended, even though they may be available in other countries, include sulfadoxine-pyrimethamine, amodiaquine, and halofantrine because of resistance and/or toxicity problems.

**Uncomplicated Non-Falciparum Malaria**

Chloroquine remains the treatment of choice for all \textit{P malariae} and \textit{P ovale} infections and for \textit{P vivax} infections acquired outside Papua New Guinea and Indonesia; hydroxynchloroquine is a second-line alternative. Currently, there are limited data on optimal treatment options for \textit{P vivax} infections acquired in areas with highly prevalent chloroquine resistance (Papua New Guinea and Indonesia). The best option may be atovaquone-proguanil, with mefloquine or quinine plus tetracycline or doxycycline as alternatives. Both quinine (3 days) and either tetracycline or doxycycline (7 days)\textsuperscript{121-128} and mefloquine\textsuperscript{129-135} have been historically used successfully in case reports or small case series. More recently, both atovaquone-proguanil, in a relatively small study,\textsuperscript{99} and mefloquine (at 15 mg/kg)\textsuperscript{136} have effectively treated \textit{P vivax} malaria in Indonesia, where high rates of CRPV exist. Of note, although initial studies of atovaquone-proguanil showed high (68\%) rates of recurrent parasitemia before 28 days of follow-up\textsuperscript{101} (some of which may have been relapses), subsequent (albeit small) studies have demonstrated excellent efficacy (\textgreater{}95\%) of atovaquone-proguanil against \textit{P vivax} malaria.\textsuperscript{99,137} Data are too limited to recommend quinine-clindamycin\textsuperscript{99} for first-line treatment of \textit{P vivax}, including CRPV, infections. Baird and colleagues demonstrated 85\% efficacy of chloroquine and high-dose (2.5 mg/kg base over 3 days) primaquine for treatment of CRPV.\textsuperscript{138} The CDC has not recommended this regimen due to relative ineffectiveness in experienced patients and suboptimal efficacy.

Infections with \textit{P vivax} or \textit{P ovale} who have been treated with primaquine should, if possible, overlap with the blood schizonticidal treatment.\textsuperscript{138-140} Patients who are not able to take primaquine should be counseled on the possibility of having a relapsing infection (estimated to be approximately 20\% [range, 5\%-80\%]) and the need to seek treatment if similar symptoms recur. Another potential option for patients unable to take primaquine who are experiencing frequent relapses is chloroquine (or mefloquine, in the case of CRPV) prophylaxis for the period of time that relapses are most likely to occur (ie, a few years). Although atovaquone-proguanil has “causal prophylactic activity” (ie, the ability to prevent blood stage infection by killing developing liver stage parasites), it does not appear to eradicate hypnozoites\textsuperscript{101,105} and may not prevent the establishment of hypnozoites.\textsuperscript{141,142} Thus, patients with \textit{P vivax} or \textit{P ovale} malaria who have been treated with atovaquone-proguanil also need primaquine. Although a modified regimen of 45 mg (base) of primaquine weekly for 8 weeks has been suggested as an alternative for patients with mild G6PD deficiency,\textsuperscript{143,144} the data on both safety and efficacy of such a regimen are very limited. Primaquine for “radical cure” (ie, primaquine used in conjunction with an effective blood schizonticide for the treatment of a patient with \textit{P vivax} or \textit{P ovale} malaria) in a known G6PD-deficient individual should be used only after a careful risk/benefit assessment and under strict medical supervision.\textsuperscript{140}

**Severe Malaria**

The single most important step in the management of severe malaria is im-
mediate initiation of appropriate parenteral treatment. In the United States, the only parenteral drug currently available is quinidine gluconate. Blood films should be examined every 12 hours until negative for malaria parasites. If parasite density typically decreases by 90% over the first 48 hours with quinine or quinidine therapy. If parasitemia over the first 48 hours with quinine or quinidine, health care professionals can considered investigational (eg, by checking the quinidine level). Quinidine levels should be maintained in the range of 3 to 8 mg/L.

Quinidine is more cardiotoxic than quinine and should be administered in an intensive care unit with continuous electrocardiographic and frequent blood pressure monitoring. Quinidine-related cardiovascular adverse effects are potentially serious and may be more frequent if the drug is administered rapidly. The risk of cardiotoxicity is increased with bradycardia, hypokalemia, and hypomagnesemia and if the patient has received other drugs that may prolong the QTc interval (eg, quinine, mefloquine, or macrolide antibiotics).

Because newer antiarrhythmic agents have displaced quinidine gluconate, quinidine is often not stocked in many hospitals. Hospital drug services should maintain or add quinidine gluconate to their formularies. If they do not stock the drug, they must be able to immediately locate a nearby source. Otherwise, the hospital should contact their local or regional distributor to request the drug or contact the Eli Lilly Co directly (telephone: 1-800-821-0538). Assistance from the company to arrange a rapid shipment of the drug is available between the hours of 6 AM and 6 PM. If further assistance is needed in managing patients with malaria, health care professionals can contact the CDC Malaria Hotline.

Because most deaths from severe malaria occur within the first 24 to 48 hours of treatment, an initial loading dose of quinidine is recommended to achieve therapeutic levels as rapidly as possible. Unless the patient has received more than 40 mg/kg quinine in the previous 2 days or has received mefloquine in the previous 12 hours (in which case the loading dose is not given but a continuous quinidine infusion is still administered). The quinidine infusion should be temporarily slowed or stopped if the QT interval increases to greater than 0.6 seconds, the QTc complex increases greater than 50%, the QTc interval is prolonged by more than 25% of the baseline value, or if hypotension unresponsive to fluid challenge develops. If significant electrocardiographic changes persist or malignant arrhythmias develop, physicians should treat the arrhythmias and consider expert consultation through the CDC Malaria Hotline or other tropical medicine experts. Options in such severe situations may include administration of alternative antimalarial drugs via nasogastric tube along with exchange transfusion. Quinidine continuous infusion should be continued during exchange transfusion.

Initial (including loading) doses of parenteral quinine or quinidine need not be reduced in persons with renal failure. The pharmacokinetic properties of the cinchona alkaloids are altered in malaria, with a contraction in the volume of distribution that is proportional to the severity of malarial illness. If renal failure persists or the patient’s clinical condition does not improve, the maintenance dosage should be reduced by one third to one half on the third treatment day.

The artemisinin derivatives clear parasites very rapidly, are now a key component of malaria treatment worldwide, and have been shown to reduce mortality in severe malaria compared with parenteral quinine. These drugs are not yet available in the United States, but the CDC hopes to make intravenous artesunate available under an Investigational New Drug protocol in 2007.

Exchange transfusion has been used in the treatment of severe malaria since 1974 with apparent benefit. Potentially due to rapid reduction of parasitemia by direct parasite removal, reduction of toxic byproducts, and/or improved rheology with transfused cells. The technical aspects of exchange transfusion have been discussed in an excellent review by Powell and Grima. However, exchange transfusion and its indications will remain controversial until a carefully controlled, adequately powered comparative study is conducted, an unlikely probability. In the decision to use exchange transfusion, the potential risks of exchange transfusion, including fluid overload, febrile and allergic reactions, metabolic disturbances, red blood cell alloantibody sensitization, transmissible infection, cerebral hemorrhage, and line sepsis, must be weighed against potential benefits. The CDC recommends that exchange transfusion be strongly considered for persons with a parasitemia higher than 10% or if complications such as cerebral malaria, nonvolume overload pulmonary edema, or renal compromise exist.

Various adjunctive treatments appear in the literature that are either unproven or are harmful in the treatment of severe malaria and are not currently recommended. They include phenobarbital for prophylaxis of seizures, dexamethasone for treatment of cerebral malaria, heparin for treatment of thrombocytopenia and/or fibrinogenemia, iron chelators that aim to reduce parasite clearance time, pentoxifylline for inhibition of tumor necrosis factor synthesis, and dichloroacetate for treatment of metabolic acidosis.
abnormalities. Pulmonary edema may be due to either fluid overload or adult respiratory distress syndrome and can be minimized by keeping patients euvoletic. Acute renal failure is generally oliguric. With dialysis, renal function can be expected to return after a median of 4 days, although some patients may require dialysis for 2 to 3 weeks.184 Thrombocytopenia is common in severe malaria. Laboratory evidence of activated coagulation is more common than is disseminated intravascular coagulation with bleeding.181,185,186 Hyponatremia, hypocalcemia, hypophosphatemia and hyperphosphatemia, and hyponagmasenia and hypermagnesemia188 have all been reported in patients with \textit{P falciparum} malaria.181

In patients with suspected cerebral malaria, a lumbar puncture should be performed to rule out bacterial meningitis, and magnetic resonance imaging or computed tomographic scans should be performed to rule out intracerebral bleeding, cerebral edema, and cerebral/medullary herniation. Most survivors with cerebral malaria regain consciousness within 2 to 3 days, although it may occasionally take more than a week.189

\textbf{Induced Malaria}

Because malaria acquired through bloodborne transmission (eg, blood transfusion or organ transplantation) has no exoerythrocytic stage, primaquine treatment is not needed in induced \textit{P vivax} or \textit{P ovale} infections.

\textbf{Self-treatment}

The CDC recommends the use of malaria prophylaxis, rather than self-treatment, for travelers to malarious areas. However, travelers who elect not to take prophylaxis, who do not choose an optimal drug regimen (eg, chloroquine for 

\textit{P falciparum} malaria), or those who require a less than optimal drug regimen are at greater risk for acquiring malaria and needing prompt treatment. Travelers who are taking effective prophylaxis but who will be in very remote areas may decide, in consultation with their clinician, to take along a dose of antimalarial medication for self-treatment. The only drug recommended for self-treatment for US travelers is atovaquone-proguanil. It should not be used in patients on atovaquone-proguanil prophylaxis because of the risk of breakthrough parasitemia due to a resistant organism in those patients. In such cases, specialized tropical medicine consultation should be sought. Quinine does have a suboptimal alternative due to potential adverse drug reactions and the complexity of the regimen. Travelers should be advised that self-treatment of a possible malaria infection is only a temporary measure and that prompt medical evaluation is imperative.4

\textbf{Malaria in Children}

Tetracycline and doxycycline have a relative contraindication for use in infants and children younger than 8 years of age due to reports of drug deposition in calcifying areas of bones and teeth that result in permanent tooth staining, enamel hypoplasia, and decreased linear skeletal growth rate180,181; clindamycin in combination with quinine should be used instead. While the US package insert recommends mefloquine for use in children older than 6 months of age,119 the drug is generally well tolerated in children weighing more than 5 kg.192-195 with vomiting as the principal adverse effect.192-196 Although few studies document the safety and tolerability of primaquine in children, the drug has been used for more than 50 years with no apparent safety problems. There is no evidence to suggest that the drug cannot be used in children of any age who do not have G6PD deficiency.140 Neither the American Academy of Pediatrics nor US4 or Canadian107 public health authorities list a lower age limit for primaquine use.

\textbf{Malaria in Pregnant Women}

Malaria infection in pregnant women is associated with high risks of both maternal and perinatal morbidity and mortality, including spontaneous abortion, stillbirth, premature delivery, low birth weight, congenital infection, and/or neonatal death. For uncomplicated \textit{P falciparum} infections acquired in regions with chloroquine-resistant strains, quinine plus clindamycin has been shown to be safe and efficacious and is recommended.65 Concerns that quinine may cause fetal toxicity or induce labor when given late in pregnancy have not been substantiated at the doses used for treatment of malaria.180 An important adverse effect of quinine in pregnant patients is hyperinsulinemia, which can precipitate or worsen hypoglycemia.188 Late in pregnancy, quinine is distributed to the fetus, raising concerns about quinine triggering insulin release and resulting in fetal hypoglycemia.182 However, the risks of untreated \textit{falciparum} malaria during pregnancy outweigh the potential risk of adverse drug effects from quinine or quinidine.

Atovaquone-proguanil or mefloquine are not currently recommended for treatment in pregnancy and should only be used if quinine plus clindamycin or quinine monotherapy is not available or is not being tolerated. Tetracycline and doxycycline are contraindicated. Although 2 recent studies of the atovaquone-proguanil and artesunate combination treatment for \textit{P falciparum} infections in pregnant women showed the regimen to be well-tolerated with no evidence of toxicity to the mother or fetus,199,200 further study is needed before atovaquone-proguanil can be recommended for use during pregnancy.

Because primaquine can potentially cause hemolytic disease in a G6PD-deficient fetus, primaquine is contraindicated in pregnancy. Pregnant women treated for \textit{P ovale} and \textit{P vivax} infections should also receive chemoprophylaxis until delivery. The prophylaxis regimen should consist of either chloroquine, 300-mg base (=500 mg salt) orally once per week; or, for \textit{P vivax} infections acquired in areas with chloroquine-resistant strains, mefloquine 228-mg base (=250 mg salt) orally once per week. While mefloquine is not recommended for malaria treatment during pregnancy,201

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eral studies support its safety as chemoprophylaxis during pregnancy.\textsuperscript{223-226} After delivery, women should be treated with primaquine as recommended for nonpregnant adult patients.

**Congenital Malaria**

There are approximately 2 cases of congenital malaria reported in the United States annually. Infants typically present at 1 to 2 months of age with fever, anemia, failure to thrive, and splenomegaly. As with induced malaria, there is no exoerythrocytic phase and thus no need for primaquine treatment in P vivax or P ovale congenital infections. For mothers who are parasitemic either during pregnancy or at delivery, clinicians should judge management of the infant in each case individually, factoring in such issues as reliability of follow-up and access to medical care. In some cases it may be appropriate to simply educate the mother about the risk of congenital malaria and instruct her to seek medical care if the baby develops symptoms of malaria. In others, presumptive treatment of the newborn may be warranted.

**Clinical Assistance and Reporting**

The CDC posts current treatment recommendations on its Web site at www.cdc.gov/malaria and has clinicians on call 24 hours to provide advice to clinicians on the diagnosis and treatment of malaria.

Malaria is a nationally notifiable disease and all cases should be reported to the appropriate state health department. Case reporting is critical to monitor trends in disease acquisition and to provide recommendations for malaria chemoprophylaxis and treatment.\textsuperscript{2,207-209}

**CONCLUSIONS**

Malaria will remain a diagnostic and treatment challenge for US clinicians as increasing numbers of persons travel to and emigrate from malarious areas. In a review of all malaria deaths in the US from 1963-2001, failure to diagnose malaria on initial presentation, promptly initiate treatment after diagnosis, and/or prescribe an appropriate antimalarial drug, were substantial contributing factors in malaria deaths.\textsuperscript{2} Clinicians must remain alert to the possibility of this disease and take immediate measures toward prompt accurate diagnosis and treatment.

**REFERENCES**

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