parasites (i.e., >20% of parasites with visible pigment) in the peripheral-blood film or by the presence of phagocytosed malarial pigment in >5% of neutrophils. In *P. falciparum* infections, gametocytemia peaks 1 week after the peak of asexual parasites. Because the mature gametocytes of *P. falciparum* (unlike those of other plasmodia) are not affected by most antimalarial drugs, their persistence does not constitute evidence of drug resistance. Phagocytosed malarial pigment is sometimes seen inside peripheral-blood monocytes or polymorphonuclear leukocytes and may provide a clue to recent infection if malaria parasites are not detectable. After the clearance of the parasites, this intraphagocytic malarial pigment is often evident for several days in the peripheral blood films or for longer in bone marrow aspirates or smears of fluid expressed after intradermal puncture. Staining of parasites with the fluorescent dye acridine orange allows more rapid diagnosis of malaria (but not speciation of the infection) in patients with low-level parasitemia.

Molecular diagnosis by polymerase chain reaction (PCR) amplification of parasite nucleic acid is more sensitive than microscopy or rapid diagnostic tests for detecting malaria parasites and defining malarial species. While currently impractical in the standard clinical setting, PCR is used in reference centers in endemic areas. In epidemiologic surveys, sensitive PCR detection may prove very useful in identifying asymptomatic infections as control and eradication programs drive parasite prevalence down to very low levels. Serologic diagnosis with either indirect fluorescent antibody or enzyme-linked immunosorbent assays may prove useful as measures of transmission intensity in future epidemiologic studies. Serology has no place in the diagnosis of acute illness.

LABORATORY FINDINGS

Normochromic, normocytic anemia is usual. The leukocyte count is generally normal, although it may be raised in very severe infections. There is slight monocytosis, lymphopenia, and eosinopenia, with reactive lymphocytosis and eosinophilia in the weeks after the acute infection. The erythrocyte sedimentation rate, plasma viscosity, and levels of C-reactive protein and other acute-phase proteins are high. The platelet count is usually reduced to ~10^5/μL. Severe infections may be accompanied by prolonged prothrombin and partial thromboplastin times and by more severe thrombocytopenia. Levels of antithrombin III are reduced even in mild infection. In uncomplicated malaria, plasma concentrations of electrolytes, blood urea nitrogen (BUN), and creatinine are usually normal. Findings in severe malaria may include metabolic acidosis, with low plasma concentrations of glucose, sodium, bicarbonate, calcium, phosphate, and albumin together with elevations in lactate, BUN, creatinine, urate, muscle and liver enzymes, and conjugated and unconjugated bilirubin. Hypergammaglobulinemia is usual in immune and semi-immune subjects. Urinalysis generally gives normal results. In adults and children with cerebral malaria, the mean cerebrospinal fluid (CSF) opening pressure at lumbar puncture is ~160 mm; usually the CSF content is normal or there is a slight elevation of total protein level (<1.0 g/L [<100 mg/dL]) and cell count (<20/μL).

TREATMENT MALARIA

(Table 248-6) When a patient in or from a malarious area presents with fever, thick and thin blood smears should be prepared and *examined immediately* to confirm the diagnosis and identify the species of infecting parasite (Figs. 248-4 through 248-9). Repeat blood smears should be performed at least every 12–24 h for 2 days if the first smears are negative and malaria is strongly suspected. Alternatively, a rapid antigen detection card or stick test should be performed. Patients with severe malaria or those unable to take oral drugs should receive parenteral antimalarial therapy. If there is any doubt about the resistance status of the infecting organism, it should be considered resistant. Antimalarial drug susceptibility testing can be performed but is rarely available, has poor predictive value in an individual case, and yields results too slowly to influence the choice of treatment. Several drugs are available for oral treatment. The choice of drug depends on the likely sensitivity of

TABLE 248-6 REGIMENS FOR THE TREATMENT OF MALARIA[a]

Type of Disease or Treatment	Regimen(s)
Uncomplicated Malaria	
Known chloroquine-sensitive strains of *Plasmodium vivax*, *P. malariae*, *P. ovale*, *P. knowlesi*, *P. falciparum*[b]	Chloroquine (10 mg of base/kg stat followed by 5 mg/kg at 12, 24, and 36 h or by 10 mg/kg at 24 h and 5 mg/kg at 48 h) ***or*** Amodiaquine (10–12 mg of base/kg qd for 3 days)
Radical treatment for *P. vivax or P. ovale* infection	In addition to chloroquine or amodiaquine as detailed above, primaquine (0.5 mg of base/kg qd in tropical regions and 0.25 mg/kg for temperate-origin *P. vivax*) should be given for 14 days to prevent relapse. In mild G6PD deficiency, 0.75 mg of base/kg should be given once weekly for 8 weeks. Primaquine should not be given in severe G6PD deficiency.
Sensitive *P. falciparum* malaria[c]	Artesunate[d] (4 mg/kg qd for 3 days) *plus* sulfadoxine (25 mg/kg)/pyrimethamine (1.25 mg/kg) as a single dose ***or*** Artesunate[d] (4 mg/kg qd for 3 days) *plus* amodiaquine (10 mg of base/kg qd for 3 days)[e]
Multidrug-resistant *P. falciparum* malaria	Either artemether-lumefantrine[d] (1.5/9 mg/kg bid for 3 days with food) ***or*** Artesunate[d] (4 mg/kg qd for 3 days) *plus* mefloquine (24–25 mg of base/kg—either 8 mg/kg qd for 3 days or 15 mg/kg on day 2 and then 10 mg/kg on day 3)[e] ***or*** Dihydroartemisinin-piperaquine[d] (2.5/20 mg/kg qd for 3 days)
Second-line treatment/treatment of imported malaria	Either artesunate[d] (2 mg/kg qd for 7 days) or quinine (10 mg of salt/kg tid for 7 days) *plus 1 of the following 3:* 1. Tetracycline[f] (4 mg/kg qid for 7 days) 2. Doxycycline[f] (3 mg/kg qd for 7 days) 3. Clindamycin (10 mg/kg bid for 7 days) ***or*** Atovaquone-proguanil (20/8 mg/kg qd for 3 days with food)
Severe Falciparum Malaria[g]	
	Artesunate[d] (2.4 mg/kg stat IV followed by 2.4 mg/kg at 12 and 24 h and then daily if necessary)[h] ***or, if unavailable,*** Artemether[d] (3.2 mg/kg stat IM followed by 1.6 mg/kg qd) ***or, if unavailable,*** Quinine dihydrochloride (20 mg of salt/kg[i] infused over 4 h, followed by 10 mg of salt/kg infused over 2–8 h q8h[i]) ***or, if unavailable,*** Quinidine (10 mg of base/kg[i] infused over 1–2 h, followed by 1.2 mg of base/kg per hour[i] with electrocardiographic monitoring)

[a]In endemic areas, except in pregnant women and infants, a single dose of primaquine (0.25 mg of base/kg) should be added as a gametocytocide to all falciparum malaria treatments to prevent transmission. This addition is considered safe even in G6PD deficiency. [b]Very few areas now have chloroquine-sensitive *P. falciparum* malaria (Fig. 248-2). [c]In areas where the partner drug to artesunate is known to be effective. [d]Artemisinin derivatives are not readily available in some temperate countries. [e]Fixed-dose coformulated combinations are available. The World Health Organization now recommends artemisinin combination regimens as first-line therapy for falciparum malaria in all tropical countries and advocates use of fixed-dose combinations. [f]Tetracycline and doxycycline should not be given to pregnant women or to children <8 years of age. [g]Oral treatment should be substituted as soon as the patient recovers sufficiently to take fluids by mouth. [h]Artesunate is the drug of choice when available. The doses in children weighing <20 kg should be 3 mg/kg. The data from large studies in Southeast Asia showed a 35% lower mortality rate than with quinine, and very large studies in Africa showed a 22.5% reduction in mortality rate compared with quinine. [i]A loading dose should not be given if therapeutic doses of quinine or quinidine have definitely been administered in the previous 24 h. Some authorities recommend a lower dose of quinidine. [j]Infusions can be given in 0.9% saline and 5–10% dextrose in water. Infusion rates for quinine and quinidine should be carefully controlled.

Abbreviation: G6PD, glucose-6-phosphate dehydrogenase.