the infecting parasites. Despite increasing evidence of chloroquine resistance in *P. vivax* (from parts of Indonesia, Oceania, eastern and southern Asia, and Central and South America), chloroquine remains a first-line treatment for the non-falciparum malarias (*P. vivax*, *P. ovale*, *P. malariae*, *P. knowlesi*) except in Indonesia and Papua New Guinea, where high levels of resistance in *P. vivax* are prevalent.

The treatment of falciparum malaria has changed radically in recent years. In all endemic areas, the World Health Organization (WHO) now recommends artemisinin-based combinations (ACTs) as first-line treatment for uncomplicated falciparum malaria. These combinations are also highly effective for the other malarias. These rapidly and reliably effective drugs are sometimes unavailable in temperate countries, where treatment recommendations are limited by the registered available drugs. Fake or substandard antimalarials are commonly sold in many Asian and African countries. Thus, careful attention is required at the time of purchase and later, especially if the patient fails to respond as expected. Characteristics of antimalarial drugs are shown in **Table 248-7**.

SEVERE MALARIA

In large studies, parenteral artesunate, a water-soluble artemisinin derivative, has reduced mortality rates in severe falciparum malaria among Asian adults and children by 35% and among African children by 22.5% compared with mortality rates with quinine treatment. Artesunate has therefore become the drug of choice for all patients with severe malaria everywhere. Artesunate is given by IV injection but can also be given by IM injection. Artemether and the closely related drug artemotil (arteether) are oil-based formulations given by IM injection; they are erratically absorbed and do not confer the same survival benefit as artesunate. A rectal formulation of artesunate has been developed as a community-based pre-referral treatment for patients in the rural tropics who cannot take oral medications. Pre-referral administration of rectal artesunate has been shown to decrease mortality risk among severely ill children in communities without access to immediate parenteral treatment. Although the artemisinin compounds are safer than quinine and considerably safer than quinidine, only one formulation is available in the United States. IV artesunate has been approved by the U.S. Food and Drug Administration for emergency use against severe malaria and can be obtained through the Centers for Disease Control and Prevention (CDC) Drug Service (see end of chapter for contact information). The antiarrhythmic quinidine gluconate is as effective as quinine and, as it was more readily available, replaced quinine for the treatment of malaria in the United States. The administration of quinidine must be closely monitored if dysrhythmias and hypotension are to be avoided. If total plasma levels exceed 8 μg/mL or the QT_c interval exceeds 0.6 s or the QRS complex widens by more than 25% of baseline, then infusion rates should be slowed or infusion stopped temporarily. If arrhythmia or saline-unresponsive hypotension develops, treatment with this drug should be discontinued. Quinine is safer than quinidine; cardiovascular monitoring is not required except when the recipient has cardiac disease.

Severe falciparum malaria constitutes a medical emergency requiring intensive nursing care and careful management. The patient should be weighed and, if comatose, placed on his or her side. Frequent evaluation of the patient's condition is essential. Adjunctive treatments such as high-dose glucocorticoids, urea, heparin, dextran, desferrioxamine, antibody to tumor necrosis factor α, high-dose phenobarbital (20 mg/kg), mannitol, or large-volume fluid or albumin boluses have proved either ineffective or harmful in clinical trials and should not be used. In acute renal failure or severe metabolic acidosis, hemofiltration or hemodialysis should be started as early as possible.

In severe malaria, parenteral antimalarial treatment should be started immediately. Artesunate, given by either IV or IM injection, is the agent of choice; it is simple to administer, safe, and rapidly effective. It does not require dose adjustments in liver dysfunction or renal failure, and it should be used in pregnant women with severe malaria. If artesunate is unavailable and artemether, quinine, or quinidine is used, an initial loading dose must be given so that therapeutic concentrations are reached as soon as possible. Both quinine and quinidine will cause dangerous hypotension if injected rapidly; when given IV, they must be administered carefully by rate-controlled infusion only. If this approach is not possible, quinine may be given by deep IM injections into the anterior thigh. The optimal therapeutic range for quinine and quinidine in severe malaria is not known with certainty, but total plasma concentrations of 8–15 mg/L for quinine and 3.5–8.0 mg/L for quinidine are effective and do not cause serious toxicity. The systemic clearance and apparent volume of distribution of these alkaloids are markedly reduced and plasma protein binding is increased in severe malaria, so that the blood concentrations attained with a given dose are higher. If the patient remains seriously ill or in acute renal failure for >2 days, maintenance doses of quinine or quinidine should be reduced by 30–50% to prevent toxic accumulation of the drug. The initial doses should never be reduced. If safe and feasible, exchange transfusion may be considered for patients with severe malaria, although the precise indications for this procedure have not been agreed upon and there is no clear evidence that this measure is beneficial, particularly with artesunate treatment. Convulsions should be treated promptly with IV (or rectal) benzodiazepines. The role of prophylactic anticonvulsants in children is uncertain. If respiratory support is not available, then a full loading dose of phenobarbital (20 mg/kg) to prevent convulsions should not be given as it may cause respiratory arrest.

When the patient is unconscious, the blood glucose level should be measured every 4–6 h. All patients should receive a continuous infusion of dextrose, and blood concentrations ideally should be maintained above 4 mmol/L. Hypoglycemia (<2.2 mmol/L or 40 mg/dL) should be treated immediately with bolus glucose. The parasite count and hematocrit level should be measured every 6–12 h. Anemia develops rapidly; if the hematocrit falls to <20%, then whole blood (preferably fresh) or packed cells should be transfused slowly, with careful attention to circulatory status. Renal function should be checked daily. Children presenting with severe anemia and acidotic breathing require immediate blood transfusion. Accurate assessment is vital. Management of fluid balance is difficult in severe malaria, particularly in adults, because of the thin dividing line between overhydration (leading to pulmonary edema) and underhydration (contributing to renal impairment). As soon as the patient can take fluids, oral therapy should be substituted for parenteral treatment.

UNCOMPLICATED MALARIA

Infections due to sensitive strains of *P. vivax*, *P. knowlesi*, *P. malariae*, and *P. ovale* should be treated with oral chloroquine (total dose, 25 mg of base/kg) or with an ATC known to be efficacious. In much of the tropics, drug-resistant *P. falciparum* has been increasing in distribution, frequency, and intensity. It is now accepted that, to prevent resistance, falciparum malaria should be treated with drug combinations and not with single drugs in endemic areas; the same rationale has been applied successfully to the treatment of tuberculosis, HIV/AIDS, and cancers. This combination strategy is based on simultaneous use of two or more drugs with different modes of action. ACT regimens are now recommended as first-line treatment for falciparum malaria throughout the malaria-affected world. These regimens are safe and effective in adults, children, and after the first trimester of pregnancy (uncertainty regarding safety currently precludes their use in the first trimester). The rapidly eliminated artemisinin component is usually an artemisinin derivative (artesunate, artemether, or dihydroartemisinin) given for 3 days, and the partner drug is usually a more slowly eliminated antimalarial to which *P. falciparum* is sensitive. Five ACT regimens are currently recommended by the WHO. In areas with multidrug-resistant falciparum malaria (parts of Asia and South America, including those with mefloquine-resistant parasites; **Fig. 248-10**), artemether-lumefantrine, artesunate-mefloquine, or dihydroartemisinin-piperaquine should be used; these regimens provide cure rates of >90%. In areas with sensitive parasites, the aforementioned combinations, artesunate-sulfadoxine-pyrimethamine, or artesunate-amodiaquine also may be