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# Pediatric Malaria in the Developing World

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**Hundreds of millions of people suffer from malaria, and more than a million children die of malaria each year. Malaria typically presents with fever and headache, but the presentation often is nonspecific. The diagnosis should be based on blood tests, and thick and thin smears are the standard means of identifying parasites. In some areas, chloroquine still is effective as treatment, but other medications are needed in most parts of the world. Patients with severe disease (altered consciousness, marked anemia, and/or respiratory distress) should begin therapy parenterally. Control measures depend on the use of insecticide-treated bednets, early identification and treatment of symptomatic individuals, and intermittent preventive therapy. Progress continues toward the development of a useful vaccine. Semin Pediatr Infect Dis 16:105-115 © 2005 Elsevier Inc. All rights reserved.**

Malaria is the most significant parasitic infection in the world and inflicts a tremendous burden on society in tropical and subtropical areas. Approximately 2 billion people live in malaria-endemic areas, and malaria causes an estimated 300 to 500 million cases of acute illness each year. Malaria's most significant impact is in sub-Saharan Africa, where it is responsible for at least 20 percent of the mortality in young children, or approximately 3000 deaths per day.<sup>1,2</sup> In areas with high malaria transmission, 30 to 50 percent of inpatient admissions and as many as 50 percent of outpatient visits can be attributed to malaria, placing a huge demand on Africa's fragile health infrastructure.<sup>3</sup>

Malaria has a strong association with poverty and imposes enormous challenges to the most vulnerable and impoverished communities. Malaria has been estimated to cost Africa more than \$12 billion US yearly, penalizing economic growth up to 1.3 percent per year. Studies in sub-Saharan Africa have demonstrated that episodes of malaria in children have a tremendous economic impact on poor families, both directly in terms of treatment costs and indirectly by rendering adult caregivers unable to carry out work and childcare duties.<sup>4-6</sup> Malaria also has been shown to compromise chil-

dren's social and cognitive development as a result of school absenteeism and residual damage associated with chronic or severe episodes of disease.<sup>7,8</sup>

Furthermore, as the world's population has become more mobile, a substantial number of cases of malaria imported into the United States and Europe are being documented, 20 percent of which are estimated to occur in patients younger than 18 years of age. Because practitioners in these nonendemic areas may be unfamiliar with presentation of the disease, difficulties with establishing a diagnosis and providing management may arise and lead to dire consequences.<sup>9-12</sup> In this article, we describe the clinical symptoms, diagnosis, and treatment of pediatric malaria in the developing world and discuss some of the practicalities of preventing and managing malaria in various settings.

## Malaria Parasite

The malaria parasite is an obligate intracellular protozoa of the genus *Plasmodium* that is transmitted primarily through the bite of an infected female *Anopheles* mosquito. The four species of this genus that infect humans are *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae*, each of which is thought to have grown to prominence initially in Africa. Notably, it is in tropical Africa that geographical areas of endemicity for malaria have remained constant for the past century and perhaps the past several centuries.<sup>13</sup>

*P. falciparum* predominates in tropical Africa, eastern Asia, Oceania, Haiti, the Dominican Republic, and the Amazon basin of South America and is responsible for the majority of incidences of severe morbidity and mortality. *P. vivax* is the

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most widespread form of malaria infection in the world and prevails in Central America, the Middle East, India, and Southeast Asia. It rarely kills, but it can cause recurring and debilitating infections. Both *P. vivax* and *P. ovale* are capable of becoming dormant in the liver, forming a hypnozoite, and causing a relapse of symptoms months to years later. *P. malariae* has the same geographical distribution as that of *P. falciparum* but has a much lower prevalence.

## Control Measures

*Plasmodium*'s complex life cycle provides a variety of opportunities to interrupt transmission and subsequent development of disease. Vector control methods target the mosquito during various stages of its life cycle. Approaches range from the disruption of breeding sites and larva control to implementation of personal and household protective measures. In the 1950s, widespread use of insecticides (eg, dichlorodiphenyltrichloroethane [DDT]) combined with reduction of vector breeding sites by swamp drainage and environmental control with engineering methods for water source protection led to a substantial reduction in mosquito populations in many subtropical regions. However, this approach was less effective in tropical Africa because of higher rates of malaria endemicity, instability in health infrastructures, limited access to medical facilities, and the emergence of resistance to insecticides.<sup>14,15</sup> This control strategy was abandoned in the 1960s. During the ensuing decades, the resurgence of malaria has reached crisis proportions, resulting from a decreased commitment to control programs in conjunction with expanding human populations, human migration, and widespread poverty. Since the 1990s, control efforts have focused more on prevention of mosquito bites through the use of insecticide-treated nets (ITNs) and on prompt recognition and effective treatment of malaria disease.<sup>16</sup>

Prevention of malaria is particularly challenging in endemic areas primarily because of socio-economic reasons. The World Health Organization (WHO) strongly advocates the use of ITNs, which have been shown to be effective in reducing the rates of child mortality from malaria in several randomized controlled trials. Substantial reductions in the rates of both childhood mortality (up to 33%) and incidence of malaria infections (up to 50%) have been demonstrated in settings of both high and low transmission of malaria, provided the nets are retreated every 6 months.<sup>17-21</sup> Because ITNs act as an insecticide in addition to a barrier to prevent mosquito bites in an individual, the community also benefits from the intervention.

Despite heavy endorsement of bednets by the Roll Back Malaria Campaign, bednet coverage in the areas of malaria risk is suboptimal, with WHO estimates as low as 10 percent. An effective bednet program is dependent on an adequate supply of nets, education, and an effective distribution and insecticide re-treatment mechanism, which are immensely difficult to achieve in areas of extreme poverty. Nonetheless, the Africa Malaria Report 2003 revealed that 18 of the 40 malaria-endemic countries in Africa now have strategic plans to improve coverage with ITNs. Furthermore, substantial

progress has been made in developing a long-lasting, insecticidal net that is factory-pretreated and does not require any retreatment, which could improve tremendously the sustainability of this control method.<sup>22</sup>

Another prevention strategy with demonstrated efficacy that has been promoted by the Roll Back Malaria Campaign is the use of intermittent presumptive or preventive treatment of malaria during pregnancy. Trials in which sulfadoxine-pyrimethamine was given two to three times during pregnancy have shown a significant decrease in pregnancy-associated malaria complications such as maternofetal death, cerebral malaria, and low-birth-weight babies.<sup>23,24</sup> However, poor compliance with this regimen unfortunately also has been demonstrated in malaria-endemic areas.<sup>25,26</sup> The use of intermittent preventive treatment (IPT) also has been studied in infants. Two trials in Tanzania demonstrated significant decreases in the reduction in incidences of clinical attacks of malaria and severe anemia when therapeutic doses of anti-malarials were given on three occasions during the first year of life that correlated with routine check-ups and immunizations.<sup>27,28</sup> Preliminary studies looking at the impact of anti-malarial administration on the immune response to vaccines demonstrate no deleterious effect on the cellular or humoral response, but additional, more rigorously controlled trials are needed.<sup>29</sup> Similarly, the use of IPT in older children also is being investigated and eventually may have a role in malaria control efforts, particularly in areas with intense seasonal transmission.<sup>30</sup>

Because mosquitoes live on or near water, environmental improvements to decrease the number of breeding sites at the household level can be accomplished by eliminating standing water. For example, standing water in old tires, urns, buckets, plastic covers, toys, or any other container should be emptied every few days. Puddles should be removed, pools should be treated, and the water should be kept circulating. Water in birdbaths, fountains, potted plant trays, and wading pools should be changed frequently. Insecticides are a valuable part of mosquito control programs at the community level and consist of both biologic and chemical methods. Larvicides target larvae in breeding sites, and mosquito adulticides kill flying mosquitoes on contact. The powerful insecticide DDT is still in use in Africa because it is affordable and available in large quantities. However, because DDT also is lethal to the environment, its use is controversial.<sup>31,32</sup>

## Clinical Presentation

### General Signs and Symptoms of Malaria

The clinical features of malaria are notoriously nonspecific, especially in children. Frequently, disease presents as a flu-like illness with fever, chills, rigors, headache, and myalgias. Vague prodromal symptoms may occur before the development of acute paroxysms of high fever and chills. In primary episodes, classically described periodic fever patterns typically are not observed unless the illness is left untreated for many days. Gastrointestinal and respiratory symptoms also are common developments, especially with *falciparum* ma-

laria in children. A study in Nigeria found that vomiting and abdominal pain are the most common gastrointestinal complaints in children, followed by decreased appetite and diarrhea.<sup>33</sup> Because these symptoms also are characteristic of an acute gastroenteritis, they may mistakenly be identified as such, particularly in nonmalaria endemic areas with returning travelers.

Physical examination commonly reveals fever, tachycardia, and tachypnea. Hepatosplenomegaly is a very common finding in chronically or recurrently infected children residing in highly endemic areas and commonly is detected in children migrating as immigrants and refugees from these areas. Jaundice, pallor, and altered mental status also may be noted and are associated more commonly with *P. falciparum* infection. Typical laboratory findings include anemia, leukopenia, thrombocytopenia, and an elevated bilirubin. Hypoglycemia also is seen frequently with falciparum malaria in children and can be the cause of severe morbidity or mortality. Hyponatremia, elevated liver enzymes, and prolonged prothrombin times also are observed frequently.

### Specific Issues With Nonfalciparum Malaria

Infections with *P. vivax* and *P. ovale* can be debilitating but typically are not fatal. Fevers can be very high and incapacitating, but parasitemia levels generally are limited to less than 2 percent, as these parasites prefer young red blood cells (reticulocytes). Tender splenomegaly and anemia are common findings in patients with chronic or recurrent disease caused by *P. vivax*. Relapses frequently occur months to years after the initial infection unless appropriate treatment to eradicate the hepatic phase of the parasite is administered. Interestingly, certain serotypes of *P. vivax* appear to have variable responses to treatment of the intrahepatic hypnozoite stage with primaquine, and rates of cure with treatment have been reported to range from as low as 30 percent to in excess of 80 percent.<sup>34</sup> Infection caused by *P. malariae* usually is mild, and the parasite generally is considered a commensal organism. However, chronic infections are typical, with disease recrudescences occasionally occurring as many as 30 to 50 years after initial infection. Chronic infection with *P. malariae* also has been associated with nephrotic syndrome, which classically does not improve with malaria chemotherapy.<sup>35</sup>

### Specific Issues With Falciparum Malaria

*P. falciparum* is the most virulent of the four species and has the highest related rates of morbidity and mortality. It has a high capacity for amplification as it can invade red blood cells of any age, resulting in high-level parasitemias. The parasite induces the host red blood cell to express on the cell's surface a protein termed a histidine-rich protein. This protein, through recognition of endothelial receptors, gives the red blood cells infected with *P. falciparum* the unique ability to sequester in the capillaries and postcapillary venules. Through this mechanism, vital organs such as the brain and kidneys may suffer impaired oxygen and nutrient exchange,<sup>36</sup> which may manifest clinically with such symptoms

as impaired consciousness, respiratory distress, and renal dysfunction. In addition to ischemic end-organ sequelae, infection with *P. falciparum* also leads to release of inflammatory mediators, such as cytokines and tumor necrosis factor, which are largely responsible for the pathophysiology of the disease. For example, abnormal macrophage activation and cytokines may be associated with heightened severity of disease and mortality.<sup>37</sup> As further evidence mounts, it is becoming clear that the host's immunological response is a key ingredient in the pathophysiology of disease.<sup>38-41</sup>

Beyond, and perhaps reflecting, the molecular factors are many host and parasite epidemiologic factors associated with expression of the disease. Many host factors, such as age, pregnancy, preexisting hemoglobinopathies (ie, sickle cell disease), and host antigenic variation, influence disease susceptibility. A specific example of host antigenic variation is observed in West Africa, where indigenous populations rarely have the Duffy group antigen (which *P. vivax* needs to obtain entry into the host's red blood cells) on their red blood cell surface. In fact, this genetic variance accounts for the very low percentage of *P. vivax* found in West Africa. Also, many "strains" of *P. falciparum* exist, and, although not well described, certain strains possibly are more pathogenic than others.<sup>42</sup> Also clear is that previous exposure to *P. falciparum* leads to a partial immunity, which, although incompletely understood, does affect disease expression.

The clinical epidemiology of malaria is fascinating and unique. Clinical patterns of malaria vary depending on the intensity of malarial transmission. In some endemic areas termed holo- or hyperendemic areas, people may receive as many as three infective bites during a 24-hour period, and malaria is present constantly throughout the year.<sup>43</sup> In these areas, children between 1 and 3 years of age receive the brunt of clinical disease and generally manifest infection with severe anemia. As transmission becomes less intense or more unstable (seasonal), the spectrum of disease expands and begins to include cerebral malaria, which predominates in older children and extends into adults. An interesting note is that even in areas of intense transmission, infants rarely manifest clinically relevant disease, possibly because of retained maternal antibodies and the inhospitable environment that fetal hemoglobin confers against the parasite.

The clinical scenarios of severe malaria with *P. falciparum* in children include coma, respiratory distress, marked anemia, and acidosis.<sup>44-46</sup> The presence of impaired consciousness and respiratory distress have been shown to be associated with a high risk of death.<sup>47,48</sup> Frequently, laboratory evaluation in severe malaria also reveals hypoglycemia, which is postulated to be secondary to increased metabolic rate and direct inhibition of gluconeogenesis by the parasite. It may be exacerbated further by the hyperinsulinemic effect of the antimalarial chemotherapeutic agents quinidine or quinine.<sup>49,50</sup>

Cerebral malaria is a common complication of infection with *P. falciparum* in children. It is characterized by altered consciousness in a patient with falciparum parasitemia in which no other cause can be elucidated. Neurologic manifestations range from a mildly depressed sensorium to a deep

coma. Opisthotonic posturing and focal motor deficits also may be apparent. Mortality rates with cerebral malaria are estimated to range from 7 to 50 percent and are highly dependent on resources, appropriateness of treatment, and ability to give supportive care.<sup>51-53</sup> Studies have demonstrated that prolonged coma, convulsions, hypoglycemia, and acidosis are predictors of death.<sup>54-56</sup> Studies also have attempted to deduce predictors of neurologic sequelae related to cerebral malaria. The depth and duration of coma and multiple convulsions were found to be the only three independent risk factors in one large prospective study in The Gambia, West Africa. The most common neurologic abnormalities identified in the study were ataxia and paresis, which had resolved in the majority of patients (all but 4.4 percent) by 6 months post-infection.<sup>57</sup>

### Congenital Malaria

Maternal malaria has important influences on newborns and infants.<sup>58</sup> Changes in the placenta have been implicated in many of the adverse pediatric outcomes.<sup>59</sup> For individuals<sup>60,61</sup> and populations,<sup>62</sup> low birth weight is a direct consequence of malarial infection during pregnancy. Premature delivery also occurs as a result of a pregnant woman's malarial infection. Actual transplacental passage of malaria parasites is not rare and is seen in approximately 7 percent of newborns in endemic areas.<sup>63</sup> Whereas most babies clear their congenital infection without consequence, others become ill. Neonatal fever and death have been linked to congenital malaria infection in endemic areas,<sup>64</sup> and congenital malaria with fever, hepatosplenomegaly, and anemia have been seen during the second month of life in nonendemic areas.<sup>65</sup> Prenatal exposure to malaria also increases the risk of developing acute malaria infection<sup>66</sup> and anemia<sup>67</sup> at 2 to 6 months of age.

### Diagnostic Tests

Microscopic examination remains the most widely available clinical test, with the thick blood smear having increased sensitivity and the thin blood smear's utility mainly being speciation. Giemsa stain produces the highest quality smears and is used in most laboratories in the United States, but it has the disadvantage of taking substantial time (ie, thick smears may take 6-8 hours and thin smears 30 minutes). Field stain can be performed more rapidly but is thought to be less sensitive. The performance of blood smears is highly variable and, although in skilled operators' hands may detect parasitemias as low as 10 parasites per microliter, generally will not detect fewer than 50 parasites per microliter consistently. However, because many malaria-endemic areas have limited access to medical care and often lack adequate laboratory facilities and skilled personnel, treatment often is administered based on clinical signs and symptoms. Unfortunately, this method is inherently fraught with inaccuracies, and inappropriate use of antimalarials occurs commonly, particularly considering how nonspecific are signs and symptoms of malaria in children.

Alternative, nonmicroscopic methods for establishing the diagnosis of malaria also have been developed and include enzyme-linked immunoassays (ELISAs) and antigen-capture, assays which detect and differentiate *P. falciparum* from nonfalciparum malaria; polymerase chain reaction (PCR), which amplifies parasite DNA or mRNA; and the quantitative buffy coat (QBC) technique, which uses a special lens to detect acridine orange-stained parasite DNA or RNA.<sup>68,69</sup> The most appealing available diagnostic tests in terms of practicality are the rapid antigen tests. These relatively inexpensive tests generally detect histidine-rich protein 2 (HRP-2) and lactate dehydrogenase isoenzymes, with the HRP-2 being a water-soluble antigen specific for *P. falciparum*. More than 10 rapid ELISA and antigen capture tests currently are available in the world market. Studies using these rapid tests in sub-Saharan Africa and Thailand have demonstrated that they are fast and easy to use, as well as sensitive and specific, especially for *P. falciparum* (test characteristics vary between tests). Their primary limitation is that they are less sensitive for nonfalciparum malaria, and under extreme environmental conditions, such as those found in many field situations, their accuracy may be adversely affected.<sup>70-72</sup>

### Therapeutic Options

Selection of the therapeutic regimen for malaria must be based on the infecting species, severity of disease, resistance patterns, and the cost and availability of medications and resources (Table 1). The three nonfalciparum malaria species, *P. vivax*, *P. ovale*, and *P. malariae*, usually are susceptible to chloroquine. However, parts of South America and Oceania, particularly New Guinea, have reported high-level *P. vivax* resistance to chloroquine.<sup>73-76</sup> In these areas, treatment with mefloquine, atovaquone/proguanil, or quinine followed by doxycycline (in children older >7 years old) may be used. In addition, artemisinin derivatives and halofantrine have superb efficacy against all three of these infecting species.<sup>34</sup> Chloroquine generally is well-tolerated but may have some associated nausea, vomiting, dysphoria, and, in dark-skinned individuals of African descent, pruritis. After the initial treatment regimen is completed, a 2-week course of primaquine could be used to effect a "radical" or complete clearing of the infection in patients with *P. vivax* or *P. ovale* malaria to eradicate liver hypnozoites. Primaquine also may cause nausea and vomiting, but more importantly, in patients with glucose-6-dehydrogenase (G-6-PD) deficiency, it can induce a severe hemolytic anemia. Standard care includes checking a G-6-PD level before initiation of primaquine. In these patients, subsequent relapses can be treated with chloroquine or an equivalent.

Selecting a treatment for *P. falciparum* malaria is dictated by the severity of the infection and the parasite's sensitivity to available antimalarial drugs. Most areas that remain "chloroquine sensitive," such as Mexico, the Caribbean, Central America, and parts of the Middle East and China, remain so because they have predominantly nonfalciparum malaria. An exception is Haiti, which is highly endemic for malaria and has strictly chloroquine-sensitive *P. falciparum*. Therefore,

Table 1 Drugs Used in the Treatment of Malaria

Disease	Drug	Pediatric Dose	Adult Dose
Chloroquine-sensitive <i>P. falciparum</i> *	Drug of choice chloroquine†	10 mg base/kg (max. 600 mg base), then 5 mg base/kg 6 hours later, then 5 mg base/kg at 24 and 48 hours	1 g (600 mg. base), then 500 mg. (300 mg. base) 6 hours later, then 500 mg. (300 mg base) at 24 and 48 hours
	Alternative atovaquone/proguanil	11–20 kg: 250 mg/100 mg (one adult tablet) qd for 3 d 21–30 kg: 500 mg/200 mg (two adult tablets) qd for 3 d 31–40 kg: 750 mg/300 mg (three adult tablets for 3 d) >40 kg: 1 g/400 mg (four adult tablets for 3 d)	1 g/400 mg (four adult tablets) qd for 3 days
Chloroquine-resistant <i>P. falciparum</i>	Drug of choice atovaquone/proguanil	Same dose as for chloroquine-sensitive <i>P. falciparum</i>	Same dose as for chloroquine-sensitive <i>P. falciparum</i>
	Common alternatives quinine sulfate plus sulfadoxine–pyrimethamine	25 mg/kg/d in 3 doses × 3–7d‡ <1 yr: 1/4 tablet once on last day of quinine 1–3 yrs: 1/2 tablet 4–8 yrs: 1 tablet 9–14 yrs: 2 tablets >14 yrs: 3 tablets	650 mg q 8 hours × 3–7 d <sup>c</sup> 3 tablets at once on last day of quinine
	or plus clindamycin or plus doxycycline§	20–40 mg/kg/d in 3 doses × 5 d 2 mg/kg/d × 7 days bid	900 mg. tid × 5 days 100 mg bid × 7 d
	Other alternatives mefloquine¶ halofantrine	<45 kg: 15 mg/kg then 10 mg/kg 12 hours later <40 kg: 8 mg/kg q 6 hours × 3 doses; repeat in 1 week 4 mg/kg/day × 3 days same dose as above	750 mg then 500 mg 12 hours later 500 mg q 6 hours × 3 doses; repeat in one week. 4 mg/kg/day × 3 days
<i>P. ovale</i> and chloroquine-sensitive <i>P. vivax</i>	Drug of choice chloroquine	Same dose as for chloroquine-sensitive <i>P. falciparum</i>	Same dose as above
	Followed by primaquine††	0.6 mg/kg base orally once a day for 14 days	30 mg base (52.6 mg salt)
Chloroquine-resistant <i>P. vivax</i> ‡‡	Drug of choice mefloquine or quinine sulfate plus doxycycline	Same dose as for chloroquine-sensitive <i>P. falciparum</i>	Same dose as for chloroquine-sensitive <i>P. falciparum</i> 15 mg base (26.3 mg salt/one tablet) orally for 14 days
	or plus sulfadoxine–pyrimethamine followed by primaquine	Same dose as for chloroquine-resistant <i>P. falciparum</i> Same as above	Same dose as for chloroquine-resistant <i>P. falciparum</i> Same dose as for chloroquine-resistant <i>P. falciparum</i>
	Drug of choice chloroquine	Same dose as for chloroquine-sensitive <i>P. falciparum</i>	Same dose as for chloroquine-sensitive <i>P. falciparum</i>
<i>P. malariae</i>	Drug of choice chloroquine	Same dose as for chloroquine-sensitive <i>P. falciparum</i>	Same dose as for chloroquine-sensitive <i>P. falciparum</i>
All Plasmodium species: parenteral therapy	Drug of choice quinidine gluconate§§¶¶	10 mg/kg loading dose IV (max. 600 mg) in normal saline slowly over 1–2 hours, followed by continuous infusion of 0.02 mg/kg/min until oral can be started	10 mg/kg loading dose IV (max. 600 mg) in normal saline slowly over 1–2 hours, followed by continuous infusion of 0.02 mg/kg/min until oral can be started
	or quinine dihydrochloride¶¶	20 mg/kg loading dose IV in 5% dextrose over 4 hours followed by 10 mg/kg over 2–4 hours q 8 hours (max. 1800 mg/day) until oral therapy can be started	20 mg/kg loading dose IV in 5% dextrose over 4 hours followed by 10 mg/kg over 2–4 hours q 8 hours (max. 1800 mg/day) until oral therapy can be started

Table 1 Continued

Disease	Drug	Pediatric Dose	Adult Dose
	Alternative Artemether***	3.2 mg/kg IM, then 1.6 mg/kg/d	3.2 mg/kg IM, then 1.6 mg/kg/d
	Chloroquine†††	Rarely recommended	Rarely recommended

\*Assume chloroquine-sensitive if exposure occurred in Central America west of the Panama Canal, Mexico, Haiti, Dominican Republic, and the Middle East except Yemen, Oman and, Iran.

†If chloroquine is not available, hydroxychloroquine sulfate is effective: 400 mg of hydroxychloroquine sulfate is equivalent to 500 mg of chloroquine phosphate.

‡In Southeast Asia, relative resistance to quinine has increased, and the treatment should be continued for 7 days.

§Not approved for use in children younger than 8 years.

¶Pediatric dose not approved by the Federal Drug Administration. Should not be given together with quinine, quinidine or halofantrine. Should not be used in areas of reported mefloquine-resistance such as the Thai–Myanmar and Thai–Cambodia borders. Common adverse effects include nausea, vomiting, diarrhea, dizziness, toxic psychosis, and seizures.

||May be effective against multidrug-resistant *P. falciparum*, but treatment failures and resistance have been reported. May lengthen PR and QTc intervals, and cardiac arrhythmias have been reported, and not recommended when using other medications known to prolong PR or QTc intervals or when mefloquine has been used for chemoprophylaxis. Cardiac monitoring is suggested during dosing. Should not be taken within one hour before, and two hours after, a meal.

\*\*Not available in the United States.

††Should not be used in patients with G6PD, and patient status should be checked in all patients prior to use.

‡‡*P. vivax* resistant to chloroquine is a significant problem in Papua-New Guinea and Indonesia. Resistance has been reported from Myanmar, India, Irian Jaya, Thailand, the Solomon Islands, Vanuatu, Guyana, Brazil, and Peru.

§§Continuous EKG monitoring, blood pressure, and glucose monitoring are recommended.

¶¶Quinidine may have greater antimalarial activity than quinine. The loading dose should be decreased or omitted in those patients who have received quinine or mefloquine. If more than 48 hours of parenteral treatment is required, the quinine dose should be reduced by one third to one-half.

|||Not available in the United States.

\*\*\*Not available in the United States. Also available in rectal suppository formulation.

†††Extreme caution must be exercised in administering parenteral chloroquine as there is a very narrow therapeutic window and overdose may result in death.

malaria acquired in all the latter areas should be assumed to be chloroquine-sensitive and, hence, chloroquine is the medication of choice. When *P. falciparum* malaria is acquired in chloroquine-resistant areas, oral quinine in conjunction with sulfadoxine-pyrimethamine commonly is used. Unfortunately, resistance to sulfadoxine-pyrimethamine has grown rapidly in parts of South America and Southeast Asia and recently has been observed in Africa.<sup>77-79</sup> Alternatively, quinine can be used with clindamycin or doxycycline (children >7 years of age).<sup>80-82</sup> Also, atovaquone-proguanil is extremely effective in the treatment of uncomplicated *P. falciparum* malaria. It recently has been approved for use as a single agent in children weighing more than 5 kg after recent clinical trials demonstrated its safety and efficacy in this young age group.<sup>83,84</sup> Although atovaquone-proguanil has become the medication of choice in the treatment of acute *P. falciparum* malaria in the United States,<sup>85</sup> the widespread use of this agent in developing countries primarily is limited by high cost. Also, researchers fear that widespread use quickly would lead to resistance, as already *P. falciparum* quickly attains resistance to either atovaquone or proguanil alone. Even with the limited use of atovaquone-proguanil since its recent approval in developed countries, several cases of clinical failure and resistance have been documented.<sup>86,87</sup>

Patients who present with severe *P. falciparum* malaria need immediate parenteral antimalarial therapy, as these infections may progress rapidly to a lethal multisystem disease. Quinine and artemisinin derivatives are considered first-line agents in developing countries, and quinidine is used in the

United States. Quinine and quinidine are alkaloids from the bark of the cinchona tree and have remained at the forefront in the antimalarial armamentarium for more than three centuries. Both of these agents have narrow therapeutic ratios and should be infused slowly to avoid the development of cardiovascular instability and hypotension. Because these agents can potentiate the hyperinsulinemic hypoglycemia seen in severe malaria, administration of a 5 to 10 percent dextrose solution is essential when therapy with quinine or quinidine is initiated. The artemisinin derivatives, artemether and artesunate, have been shown to have comparable efficacy with quinine in moderately severe and severe malaria and actually may decrease parasitemia more rapidly. In randomized trials conducted in Africa, both intramuscular and rectal administration of artemisinin compounds proved effective.<sup>88,89</sup>

Patients with severe malaria must be monitored closely. Hypoglycemia, hypovolemia, lactic acidosis, and severe anemia all must be managed with appropriate supportive therapies. Seizures may be treated with anticonvulsants<sup>90</sup> and in patients with renal compromise, appropriate adjustments in drug doses and fluid administration are necessary. If feasible, the response to therapy should be monitored with blood smears that quantify parasite load. If parasite counts do not decrease by a minimum of 75 percent within 48 hours of the initiation of therapy, an alternative antimalarial agent should be selected.<sup>91,92</sup> Because of a lack of objective data, effectiveness and safety of exchange transfusion have been debated, with exact criteria for initiating therapy being unclear. Some

authorities have suggested exchange transfusion may be beneficial in any severely ill patient with a parasitemia that exceeds 15 percent or in any patient with parasitemia in the range of 5 to 15 percent with signs of poor prognosis.<sup>91</sup>

## Practicalities of Dealing with Malaria in Varied Settings

### Diagnosis and Treatment

The vast majority of the burden of malaria disease occurs in resource-depleted areas in vulnerable populations. The medical systems in these areas are taxed to the extreme, as these areas tend to have overall high prevalence of other resource draining diseases such as human immunodeficiency virus (HIV). In such settings, clinicians frequently treat malaria empirically with inexpensive, although frequently ineffective, antimalarial medications. For example, in Africa where chloroquine resistance rates may exceed 80 to 90 percent in some areas, *P. falciparum* frequently is treated with chloroquine. An interesting note is that patients who are partially immune, such as adults who have had malaria multiple times, actually may have symptomatic improvement because of chloroquine's antiinflammatory and immunomodulatory properties. On the other hand, chloroquine used in these high-resistance settings in nonimmune patients such as the small child or the malaria-naïve traveler may fail, with catastrophic results. Sulfadoxine-pyrimethamine also frequently is used as a single agent in sub-Saharan Africa, although, as mentioned, increasing resistance rates are worrisome. In fact, reports from Liberia indicate that rates of resistance to sulfadoxine-pyrimethamine may exceed 50 percent.<sup>93</sup>

Establishing a diagnosis in these settings currently demands a trained microscopist and technologist as well as equipment such as slides, staining materials, and a microscope. Many unanticipated issues, such as intermittent power supply and equipment degradation caused by the tropical environment (ie, mold growing in the microscope), that arise in tropical settings may hamper even the most basic blood smear reading. The relatively new rapid diagnostic tests offer potential benefits in these settings, given that they can be made to perform reliably in field conditions and can be produced and made available and affordable in developing endemic areas.

Severe malaria is especially challenging in resource-poor settings and may be limited by seemingly minor issues such as lack of intravenous catheters and noninvasive monitoring equipment. In these settings, medications such as the artemisinin derivatives, which can be administered intramuscularly or per rectum, can be a great advantage, particularly in small children. Intramuscular quinine also has been used successfully in these settings and may be used if no other alternatives are available. Although not an ideal approach, in areas with limited access to intravenous therapy, oral therapy frequently is used with an antiemetic for the vomiting but awake child, or oral therapy is administered via a nasogastric tube in the unconscious child. When intravenous catheters are available, the parenteral route of administration of qui-

nine or an artemisinin derivative is the route of administration of choice. In Haiti, one of the last bastions of chloroquine-sensitive *P. falciparum*, intravenous chloroquine still occasionally is used, although extreme caution must be exercised as the therapeutic window is very narrow and overdose can be fatal. In areas where intravenous therapy can be given, the patient still should be changed to oral therapy as soon he or she is able to swallow.

Close monitoring is essential, and in most settings, basic vital signs, such as temperature, heart rate, blood pressure, and respiratory rate, can be monitored. These observations allow the clinician to identify onset of complications such as hypoglycemia, shock, metabolic acidosis, and pulmonary edema. Some experts recommend using tepid sponge baths and antipyretics to reduce the body temperature to less than 39° C.<sup>91</sup> Blood pressure should be monitored closely when initiating quinine or quinidine because hypotension frequently occurs, necessitating slowing the drug infusion. When available, an electrocardiogram should be checked periodically to monitor for QT interval prolongation when parenteral quinine or quinidine is being used; the rate of infusion should be decreased if the QT interval increases by greater than 25 percent.

Frequent monitoring of blood glucose, especially in children, is imperative. When possible, initial hypoglycemia should be treated with a glucose infusion, and a maintenance glucose drip (5-10 percent dextrose) should be maintained throughout parenteral therapy, as hypoglycemia can develop even days after initiation of therapy. Urine output may be observed for change in quality or quantity, heralding such entities as Black Water Fever (black urine) and oliguric renal failure, both of which predict poor outcome. Hemoglobin and other serum chemistries such as electrolytes, liver, and renal function tests may be followed as availability dictates. The Blantyre coma scale may be used to monitor neurologic status.<sup>94</sup> Intermittent blood smears with quantification should be followed, and if the parasitemia is not responding should be followed, and if the parasitemia is not responding drug failure/resistance should be considered and an alternative agent employed. Because the clinical presentations of malaria and other serious illnesses can overlap and malaria can coexist with other conditions, consideration of meningitis and sepsis is important in a seriously ill febrile child.

Paradoxically, in resource-rich areas where malaria is seen infrequently, the major determinant of the patient's outcome is whether the diagnosis of malaria is considered by the clinician and correct diagnosis and treatment pursued. Three studies from nonendemic malaria settings suggest that malaria is misdiagnosed on initial presentation in 40 to 50 percent of cases.<sup>95-97</sup> Further, the Centers for Disease Control and Prevention has estimated that more than 80 percent of the deaths from malaria that occurred in the United States during the last several decades were preventable and were caused by lack of or improper malaria chemoprophylaxis in travelers, delay in establishing the diagnosis or misdiagnosis, and/or inappropriate therapy.<sup>85</sup>

### Pretravel Counseling/Intervention

Many families travel with children from nonendemic to endemic malaria areas. All family members should receive

counseling on avoiding mosquitoes and should be placed on a malaria chemoprophylactic medication when traveling to a malaria-endemic area. Children should wear protective, tight-knit clothing, and caregivers should be advised against using scented soaps and shampoos. Clothing should be permeated with permethrin before travel, which will protect areas under clothing from biting insects for several weeks, even if the clothing is laundered. A repellent containing a 25 to 50 percent concentration of N,N-diethyl-meta-toluamide (DEET) should be used on exposed skin surfaces, and ITNs should be used over sleeping quarters during the evening and nighttime hours, which correlate with biting preferences of the *Anopheles* vector.

Decisions regarding which malaria chemoprophylactic agent to employ are dependent on many factors such as cost, convenience of dosing, age, history of allergy, duration of travel, and destination. Chloroquine still may be used with travel to the chloroquine-sensitive areas previously mentioned. Three alternative first-line options are available for travelers to chloroquine-resistant areas: mefloquine, doxycycline, and atovaquone-proguanil. Mefloquine has the advantage of being approved for children of all ages and is administered once a week. Doxycycline is available to only children older than 7 years of age (12 years in the U.K.) and is a daily medication. Atovaquone-proguanil is an effective daily medication. It has minimal adverse effects, generally is well tolerated, and is approved for prophylactic use in children weighing greater than 11 kg. Primaquine is the newest chemoprophylactic agent approved in the United States and is considered a second-line chemoprophylactic option when other prophylactic agents are not available.<sup>98</sup>

## Future Possibilities

The major preventive strategy being used by the WHO in the "Roll Back Malaria" campaign is effective use of ITNs. ITNs have been estimated in endemic areas to reduce the risk of a child dying of malaria by 20 percent and to decrease clinical episodes by 50 percent.<sup>99</sup> Each ITN in use is estimated to cost between \$3 to \$15 US. The WHO Roll Back Malaria Abuja Conference set a goal of 60 percent ITN coverage of high-risk groups in Africa by 2005.<sup>100</sup> This approach has been estimated to cost \$160 million U.S. per year in materials alone but would be an important and relatively inexpensive intervention program. The successful attainment of this 60 percent coverage goal rests on two key elements laid out by the WHO: sustained subsidies targeted to highly vulnerable groups and a strengthened and expanded commercial market that decreases the cost of ITNs through competition.

Another tactic in the attempt to curb the expansion of malaria is to institute early diagnosis and prompt treatment, which not only would benefit the individual but would lead to less opportunity for the infected person to spread disease, as well as decrease emergence of resistance. Treatment options must be safe, effective, affordable, and acceptable to the population at risk. In 2000, the WHO reviewed the use of antimalarial drugs, and new recommendations for national antimalarial policies were drafted. The bedrock of these new

**Table 2 Antimalarial Combination Medications as Proposed by WHO**

<b>Nonartemisinin-based combinations</b>
Chloroquine plus sulfadoxine-pyrimethamine
Amodiaquine plus sulfadoxine-pyrimethamine
Atovaquone plus proguanil (Malarone®)
Mefloquine plus sulfadoxine-pyrimethamine (Fansimef®)
Quinine plus doxycycline or tetracycline
<b>Artemisinin-based combinations</b>
Artesunate plus chloroquine
Artesunate plus amodiaquine
Artesunate plus sulfadoxine-pyrimethamine
Artesunate plus mefloquine
Artemether plus lumefantrine (Coartem®, Ramet®)
<b>Pipeline-based combinations</b>
Piperaquine plus dihydroartemisinin-trimethoprim (Artecom®)*
Artecom® plus primaquine (CV8®)
Pyronaridine plus artesunate*
Naphthoquine plus dihydroartemisinin*
Chlorproguanil-dapsone plus artesunate (CDA®, Lapdap plus®)*

\*Limited pharmacologic or clinical data exist for at least one component or the use as a combination therapy.

treatment recommendations is implementation of a combination antimalarial treatment with the following goals: ensure rapid and long-lasting clinical cure, prevent progression of uncomplicated malaria to severe disease and death, shorten the duration of clinical episodes and associated severe anemia, and, importantly, delay the development and spread of resistance to antimalarial medications. The concept of combination therapy is based on the fact that two agents will act synergistically or at least additively. In addition, the hope is that through the improved efficacy, the parasite will be unable to develop resistance to any individual component. Combination therapy uses two or more blood schizonticidal medications with distinct mechanisms of action. Many combination therapies have been proposed (Table 2), and since the recommendations were issued, several studies have shown that success slowing emergence of resistance with new combinations can be achieved,<sup>101</sup> as well as that older medications in areas with high resistance could be reintroduced.<sup>102</sup> An interesting new compound is the combination of chlorproguanil and dapsone (Lapdap®), which is inexpensive to produce and has a short half-life, presenting a smaller "window" for selection of resistance.<sup>103</sup>

The development of a safe and effective vaccine is the goal for malaria control and will be the key to eventual eradication. Unfortunately, malaria, with its complex life cycle and varied human immunologic response, presents a great challenge to researchers. The most advanced vaccine is RTS, given with an adjuvant called ASO2. This vaccine has shown some success in the sporozoite challenge model of human infection and limited, short-term efficacy in a field trial in The Gambia. The vaccine appears to protect approximately 50 percent of recipients for about 2 months.<sup>104</sup> Many other vaccine candidates are being investigated, and a vigorous effort

to discover new potential vaccines is underway.<sup>105–107</sup> However, it likely will be many years before an effective and safe vaccine is available to the developing world.

## Conclusion

Malaria continues to have a profound impact on the health of children around the world, especially in sub-Saharan Africa, where its high mortality rate and hindrance to economic growth and development are appalling. Eradication efforts were abandoned in the 1960s and most likely will not be revisited until an effective vaccine is developed and available for widespread distribution. Control efforts are thus presently dependent on the prompt establishment of diagnosis and administration of appropriate treatment of disease as well as prevention of infection through available tools, such as ITNs, and the use of intermittent preventive treatment in pregnancy and possibly also in infants and children. Unfortunately, drug resistance is multiplying and the development of new therapeutic agents is scarce because of underfunding in malaria research. Furthermore, health systems in areas of high endemicity are overburdened and often poorly equipped to adhere to recommended protocols for prevention, diagnosis, and treatment. These unfortunate circumstances and obstacles combine to paint a grim picture indeed, which emphasizes the need for focused, creative strategies to improve the use of currently available control methods. To reduce substantially the rates of morbidity and mortality from malaria in children, we must strengthen the capacity and quality of healthcare systems at the community level in endemic areas, and the development of an effective method for the distribution and maintenance of ITNs should be a top priority. Compliance with the recommendations for intermittent preventive treatment during pregnancy also should be emphasized, and further investigative work regarding the use of intermittent preventive treatment in infants and children is needed. Alternative, practical diagnostic techniques also are essential to ensure accurate and prompt establishment of diagnosis, especially in rural areas, and innovative treatment strategies such as combination therapies using two or more antimalarial medications with differing mechanisms of action are imperative to halt the progression of resistance. However, resources for executing these strategies are costly and will depend on financial and technical contributions from wealthy countries, as well as public-private partnerships, to assist with implementation and sustainability.

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