Diagnosis and Treatment of Malaria in Children

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Malaria continues to be a problem for children returning or immigrating to industrialized countries from tropical regions. Proper diagnosis begins with clinical suspicion. In nonimmune children, malaria typically presents with high fever that might be accompanied by chills and headache. Symptoms and signs may be more subtle in partially immune children, and anemia and hepatosplenomegaly may also be present. Children may present with respiratory distress and/or rapidly progressing cerebral malaria that manifests as altered sensorium and, sometimes, seizures. Thick blood smears help to determine when infection is present, but a single smear without parasites is not sufficient to rule out malaria. Thin blood smears aid in identifying the species of parasite. Treatment must include careful supportive care, and intensive care measures should be available for treating children with complicated Plasmodium falciparum malaria. Medical regimens can include mefloquine, atovaquone-proguanil, sulfadoxine-pyrimethamine, quinine or quinidine, clindamycin, doxycycline, chloroquine, and primaquine.

Malaria is a devastating infection that annually affects >300 million people worldwide, resulting in >3000 pediatric deaths per day [1–3]. In fact, malaria is the leading cause of mortality among children <5 years of age in Africa and is the cause of ~20% of all-cause mortality in this age group [1]. Despite the availability of good preventive measures [4], >10,000 cases of malaria were reported in US civilian travelers during 1985–2001 [5]. Furthermore, an estimated 20% of cases of malaria imported to the United States and Europe occur in patients <18 years of age [6–9]. In areas where malaria is not endemic, medical practitioners are frequently unfamiliar with the disease, and delays in diagnosis and treatment are common [10–12]. Given the life-threatening potential of this illness, increased awareness and knowledge of proper management is necessary. Here, we provide a brief overview of the current approach to the diagnosis and treatment of malaria, with special attention to treatment of patients who, after recent travel or migration, present with malaria in an area where malaria is not endemic.

MALARIA PARASITE LIFE CYCLE AND EPIDEMIOLOGY

The 4 Plasmodium species that infect humans (Plasmodium falciparum, vivax, ovale, and malariae) are usually transmitted by anopheline mosquitoes. Both P. vivax and P. ovale can become dormant in the liver, forming hypnozoites that may emerge months to years after initial infection to cause disease. Infection caused by P. falciparum is associated with the greatest morbidity and mortality. The clinical severity of P. falciparum malaria is highly dependent on the malaria-specific immune status of the infected individual.

CLINICAL PRESENTATION

It has been reported that >60% of malaria is misdiagnosed at initial presentation in areas where malaria is not endemic [11]. Furthermore, up to 80% of malaria-related deaths in the United States have been deemed preventable and have been attributed to inappropriate chemoprophylaxis, delay in diagnosis, or inappropriate treatment [7]. Clinicians should routinely obtain a relevant travel history from the caretakers of any ill child. Malaria is, however, occasionally transmitted by mosquitoes in areas where it is not endemic [13], as well as through blood transfusions [14] or transplacentally [15], and the lack of his-
tory of travel to an area where malaria is endemic does not exclude the diagnosis.

**GENERAL PRESENTATION**

Patients with *P. falciparum* malaria present with high fever that may be accompanied by chills, rigors, sweats, and headache. Other common findings include generalized weakness, backache, myalgias, vomiting, and pallor. In children, these symptoms resemble and are frequently mistaken for a viral syndrome or acute gastroenteritis. Children who are partially immune (e.g., newly arrived immigrants or refugees from areas where malaria is highly endemic) frequently present with signs such as hepatosplenomegaly, anemia, and jaundice. It is not unusual for these patients to have very minimal symptoms, such as anorexia or decreased activity, or even to be asymptomatic. A recent study of Liberian children immigrating to Minnesota found that smears of blood from 28 of 43 patients were positive for malaria parasites. Of children with positive test results, one-third were asymptomatic, and splenomegaly was the only manifestation of disease in one-third [16].

In addition to specific tests for malaria, several other non-specific laboratory abnormalities are common in patients with this disease, such as elevated C-reactive protein levels, elevated procalcitonin levels, thrombocytopenia, neutropenia, and elevated liver enzyme levels. Although it is unusual in the travel population, the partially immune patient may have additional laboratory abnormalities on presentation, such as anemia, hypoalbuminemia, and hematuria. Hypotension and hypoglycemia deserve special mention, because they are associated with more-severe morbidity and occur more commonly in children than in adults [17].

Although *P. falciparum* generally manifests days to weeks after initial exposure, *P. vivax* and *P. ovale*, which have the hepatic hypnozoite stage, may present much later. Patients with *P. vivax* infection commonly present with paroxysmal fevers, chills, headaches, and myalgias. In chronically infected children, anemia and hypersplenism are common. Splenic rupture is a serious complication in children with hypersplenism. *P. malariae* and *P. ovale* generally cause fever but not a toxic appearance. In some individuals, *P. malariae* may coexist as a commensal organism, causing infection but no clinical disease.

Malaria frequently occurs in patients who have a history of recent or ongoing use of a malaria chemoprophylactic agent. This may be attributed to several factors, such as drug resistance, noncompliance with treatment, or inadequate or inappropriate administration (especially in children, because of the difficulties in administering bitter medications). It may be very difficult to diagnose malaria in these children, because they may have minimal symptoms and malaria blood smears are frequently falsely negative. Malaria should be considered and the diagnosis diligently pursued under these circumstances.

**COMPLICATED *P. FALCIPARUM* MALARIA**

Many factors influence a patient’s risk of developing severe malaria, particularly the species of malaria parasite and the patient’s immune status, which depends on previous exposure to malaria. As noted, *P. falciparum* is the most virulent of the plasmodia. Complications of *P. falciparum* infection are the result of cytokine release and of the parasite’s unique ability to cause parasitized RBCs to adhere to vascular endothelium and cause RBC sequestration, altered blood flow, and ischemia. The patient’s immune status also greatly affects the manifestations of malaria. In populations originating from areas of constant, high-intensity malaria transmission, most mortality occurs among younger children, as a result of severe anemia. In the same populations, infected adults and older children may have minimal symptoms or may be asymptomatic [18].

Conversely, in areas where malaria is less prevalent, partial immunity may not develop, or it may develop at an older age. In these cases, as is true for nonimmune travelers, the major cause of mortality is cerebral malaria. Headache, confusion, and irritability may precede cerebral malaria, but a nonimmune child’s condition can precipitously decline from normal sensorium to coma within hours [19]. Seizures are common, and children, as opposed to adults, frequently have increased intracranial pressure [20, 21]. Other typical findings include decorticate or decerebrate posturing, mydriasis, dysconjugate gaze, papilledema, retinal hemorrhages, and altered respiration [20]. The findings of examination of CSF are generally unremarkable (WBC count of <20 cells/µL, slightly elevated protein level, and normal glucose level). Imaging studies may reveal nonspecific findings that are consistent with cerebral edema or ischemia. Before a conclusive diagnosis of cerebral malaria can be made, it is imperative that other causes of neurologic decline be excluded, even when *P. falciparum* parasitemia has been detected [18, 20].

Hypoglycemia, an important complication of severe malaria in children, results from parasite-induced suppression of gluconeogenesis in the liver and induction of insulin secretion from the pancreas. The excess secretion of insulin is intensified by the initiation of quinine treatment and can result in devastating neurologic sequelae. Respiratory distress is another common complication in children, but, unlike in adults, it is rarely primarily the result of pulmonary edema or respiratory distress syndrome and instead usually is a consequence of severe acidosis. Black water fever (severe hemolysis, hemoglobinuria,
and renal failure) and algid malaria (vascular collapse, shock, and hypothermia) are rare presentations in children.

**DIAGNOSIS**

**Diagnostic techniques.** Diagnostic tests for malaria include standard thick and thin blood smears, rapid antigen detection tests, PCR, and antibody tests. Thick and thin blood smears remain the most widely available and used tests, particularly in the United States. Thick blood smears test for the presence or absence of parasites, and thin blood smears allow speciation and quantification. The sensitivity and specificity of blood smears vary greatly and are influenced by many factors, such as laboratory skill, timing and quality of smear collection, and level of parasitemia [22, 23]. Most skilled laboratory personnel can detect parasite levels as low as ~50 parasites/µL of blood. One set of negative thick and thin blood smears is never sufficient to exclude malaria, even when prepared by the most skilled hands, but 3 sets of negative blood smears are generally considered sufficient, although additional smears may be necessary in some cases.

Many rapid antigen tests are available outside the United States. Most of these tests will differentiate between *P. falciparum* and nonfalciparum infections through the detection of histidine-rich proteins and/or parasite lactate dehydrogenase. These tests have shown mixed results in multiple trials, but several seem to compare favorably with blood smears when performed by trained personnel under laboratory conditions [24, 25].

PCR tests are felt to be at least as sensitive and specific as the traditional blood smear [26–29] and can detect parasite levels of ≤1 parasite/µL. In the United States, the use of PCR is clinically limited, because the tests generally are only available from specialized, government-sponsored laboratories. In addition, PCR results may continue to be positive for >1 week after treatment because of persistence of antigen in the serum. Currently, PCR is used mainly to confirm positive blood smears and is valuable in identification of malaria species, particularly when the results of smears are not definitive or there is a mixed infection.

The detection of antibodies is not useful in the diagnosis of acute malaria, and in the United States, such a test may only be obtained from the US Centers for Disease Control and Prevention under special circumstances. This test is used in 2 common scenarios. First, antibody detection is used when the patient is a newly arrived immigrant or refugee with tropical splenomegaly (hyperactive malarial splenomegaly). “Tropical splenomegaly” is a term that has traditionally been used to describe individuals who have a large spleen, are suspected of having chronic malaria, and have multiple blood smears that are negative for malaria parasites. In this cohort, antibody (IgM) levels are markedly elevated, and IgM levels and splenomegaly decrease after presumptive antimalarial treatment. Second, antibody detection is used when the patient is a returned traveler with a history of malaria diagnosis and treatment during recent travels and serologic confirmation is desired. It is interesting to note that evidence suggests that travelers who have received a diagnosis of malaria while in the tropics frequently were given an incorrect diagnosis [30].

**Diagnostic approach to the patient.** When evaluating a nontoxic child with suspected malaria, the clinician must answer 2 questions. First, was the patient in an area where *P. falciparum* malaria is endemic? A nontoxic-appearing child who is exposed only to nonfalciparum malaria may receive outpatient evaluation if no other serious infection is suspected. Second, if the patient has been exposed to falciparum malaria, is he or she partially immune? For clinical purposes, children may be considered to be partially immune if they are >6 years of age, have a history of malaria, and have recently resided in an area where malaria is highly endemic. Such children generally are new immigrants or refugees. Prompt and thorough evaluation is necessary, but outpatient evaluation and treatment may be sufficient if caregivers are deemed to be reliable and the child does not appear toxic. A nonimmune, febrile child who may have been exposed to *P. falciparum* represents a medical emergency; an aggressive inpatient evaluation should be performed, regardless of the child’s appearance (figure 1). A toxic-appearing child with a history of malaria exposure should be admitted to an intensive care unit, and aggressive diagnosis and treatment should be pursued. Appropriate laboratory work must be performed, including blood smears for malaria parasites, and empirical parenteral antimalarial therapy must be initiated. If no parasites are seen on initial smears, follow-up smears should be obtained every 8 h if there is continued concern about malaria. A child who emigrates from a holoendemic malarious area has a significant chance of having a positive blood smear, and the presence of malaria parasitemia does not preclude the possibility of other, coexisting illnesses.

**TREATMENT**

Treatment for malaria must be selected on the basis of the infecting *Plasmodium* species, the severity of disease, the drug susceptibility of the infecting parasites, and the availability of medications and resources. The severity of illness will influence the drug selected and the route of administration (figure 2).

**Treatment of *P. falciparum* Malaria**

*P. falciparum* malaria may be classified as uncomplicated or complicated. Complicated malaria may be suspected when a patient at risk of malaria presents with altered mental status, respiratory distress, signs or symptoms of shock, seizures, gross hematuria, or severe laboratory abnormalities, including aci-
Figure 1. Clinical approach to patients with suspected malaria. A patient should be considered to be partially immune if he or she is >6 years of age, has a history of malaria infection, and has recently (<2 years before presentation) resided in an area where malaria is highly endemic. A rapid test may become a useful addition to diagnosis. ICU, intensive care unit.

dementia, profound anemia, signs of disseminated intravascular coagulation, or hyperparasitemia (on the basis of the percentage of RBCs that are infected: >2% in nonimmune children and >10% in partially immune children). Caution must be exercised, particularly in the United States, when a clinician is notified of hyperparasitemia in an apparently well-appearing child. Although this finding may occur in partially immune children, it is more frequently the result of a laboratory error.

Managing uncomplicated *P. falciparum* malaria. Oral quinine (or quinidine, if quinidine is more readily available) plus sulfadoxine-pyrimethamine has been suggested as the first line of therapy for uncomplicated chloroquine-resistant *P. fal-

Figure 2. Treatment approach to patients with laboratory-confirmed malaria. In children >7 years of age. If *Plasmodium vivax* is acquired in an area of high chloroquine resistance (e.g., New Guinea), alternative therapy may be necessary. G6PD, glucose-6-dehydrogenase; ICU, intensive care unit; ID, infectious diseases; SP, sulfadoxine-pyrimethamine. 

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<table>
<thead>
<tr>
<th>Pathogen, drug</th>
<th>Pediatric dosage</th>
<th>Adult dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chloroquine-sensitive <em>Plasmodium falciparum</em></strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First choice: chloroquine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10 mg of base/kg (maximum, 600 mg of base), then 5 mg of base/kg 6 h later, then 5 mg of base/kg at 24 and 48 h</td>
<td>1 g (600 mg of base), then 500 mg (300 mg of base) 6 h later, then 500 mg (300 mg of base) at 24 and 48 h</td>
</tr>
<tr>
<td>Alternative: atovaquone-proguanil</td>
<td>11–20 kg: 250/100 mg (1 adult tablet) qd for 3 days 21–30 kg: 500/200 mg (2 adult tablets) qd for 3 days 31–40 kg: 750/300 mg (3 adult tablets) qd for 3 days &gt;40 kg: 1 g/400 mg (4 adult tablets) qd for 3 days</td>
<td>1 g/400 mg (4 adult tablets) qd for 3 days</td>
</tr>
<tr>
<td><strong>Chloroquine-resistant <em>P. falciparum</em></strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First choice: atovaquone-proguanil</td>
<td>Same dose as for chloroquine-sensitive <em>P. falciparum</em></td>
<td>Same dose as for chloroquine-sensitive <em>P. falciparum</em></td>
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<tr>
<td>Common alternative: quinine sulfate</td>
<td>25 mg/kg/day in 3 doses for 3–7 days&lt;sup&gt;c&lt;/sup&gt;</td>
<td>650 mg q8h for 3–7 days&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Plus sulfadoxine-pyrimethamine</td>
<td>&lt;1 year of age: 1/4 tablet once on last day of quinine 1–3 years of age: 1/2 tablet 4–8 years of age: 1 tablet 9–14 years of age: 2 tablets &gt;14 years of age: 3 tablets</td>
<td>3 tablets at once on last day of quinine</td>
</tr>
<tr>
<td>Or plus clindamycin</td>
<td>20–40 mg/kg/day in 3 doses for 5 days</td>
<td>900 mg t.i.d. for 5 days</td>
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<tr>
<td>Or plus doxycycline&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2 mg/kg/day for 7 days</td>
<td>100 mg b.i.d. for 7 days</td>
</tr>
<tr>
<td><strong>Other alternatives</strong></td>
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<tr>
<td>Mefloquine&lt;sup&gt;e&lt;/sup&gt;</td>
<td>&lt;45 kg: 15 mg/kg, then 10 mg/kg 12 h later 45 kg: 8 mg/kg q6h for 3 doses; repeat in 1 week 40 mg/kg/day for 3 days</td>
<td>750 mg, then 500 mg 12 h later 4 mg/kg/day for 3 days</td>
</tr>
<tr>
<td>Halofantrine&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Same dosages as above</td>
<td>Same as for chloroquine-sensitive <em>P. falciparum</em></td>
</tr>
<tr>
<td>Artesunate&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Same dosages as above</td>
<td>Same as for chloroquine-sensitive <em>P. falciparum</em></td>
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<tr>
<td>Artesunate plus mefloquine</td>
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<tr>
<td><strong>Plasmodium ovale</strong> and chloroquine-sensitive <em>Plasmodium vivax</em>**: chloroquine followed by primaquine&lt;sup&gt;h&lt;/sup&gt;</td>
<td>Same as for chloroquine-sensitive <em>P. falciparum</em> (0.3 mg of base/kg/day po for 14 days</td>
<td>Same as for chloroquine-resistant <em>P. falciparum</em></td>
</tr>
<tr>
<td><strong>Chloroquine-resistant <em>P. vivax</em></strong>&lt;sup&gt;i&lt;/sup&gt;</td>
<td></td>
<td></td>
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<tr>
<td>First choice</td>
<td>Mefloquine followed by primaquine</td>
<td>Same as for chloroquine-resistant <em>P. falciparum</em></td>
</tr>
<tr>
<td>Quinine sulfate plus doxycycline followed by primaquine</td>
<td>Same as for chloroquine-resistant <em>P. falciparum</em></td>
<td>Same as for chloroquine-resistant <em>P. falciparum</em></td>
</tr>
<tr>
<td>Quinine sulfate plus sulfadoxine-pyrimethamine followed by primaquine</td>
<td>Same as for chloroquine-resistant <em>P. falciparum</em></td>
<td>Same as for chloroquine-resistant <em>P. falciparum</em></td>
</tr>
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<sup>a</sup> downloaded from https://academic.oup.com/cid/article-abstract/37/10/1340/451166 by guest on 13 August 2018

<sup>b</sup> chloroquine follows the path of the initial combination regimen.

<sup>c</sup> Quinine is administered either as a continuous intravenous infusion or in alternate dose regimens.

<sup>d</sup> Doxycycline is administered at a dose of 2 mg/kg/day in 3 divided doses for 7 days.

<sup>e</sup> Mefloquine is administered at a dose of 25 mg/kg/day in 3 divided doses for 5 days.

<sup>f</sup> Halofantrine is administered at a dose of 15 mg/kg, then 10 mg/kg 12 h later.

<sup>g</sup> Artesunate is administered at a dose of 4 mg/kg/day for 3 days.

<sup>h</sup> Primaquine is administered at a dose of 0.3 mg of base/kg/day po for 14 days.

<sup>i</sup> Chloroquine-resistant *P. vivax* is treated with the same regimens as for chloroquine-resistant *P. falciparum*.
**Plasmodium malariae:** chloroquine  
Same as for chloroquine-sensitive *P. falciparum*  
Same as for chloroquine-sensitive *P. falciparum*

<table>
<thead>
<tr>
<th>All <em>Plasmodium</em> species: parenteral therapy</th>
<th>First choice</th>
<th>Alternatives</th>
</tr>
</thead>
</table>
| Quinidine gluconate<sup>1k</sup>          | 10 mg/kg loading dose iv (maximum, 600 mg) in normal saline, administered slowly over the course of 1–2 h, followed by continuous infusion of 0.02 mg/kg/min until oral therapy can be initiated | Artemether<sup>l</sup>  
3.2 mg/kg im, then 1.6 mg/kg/day |
| Quinine dihydrochloride<sup>9k</sup>       | 20 mg/kg loading dose iv in 5% dextrose, administered over the course of 4 h, followed by 10 mg/kg administered over the course of 2–4 h q8h (maximum, 1800 mg/day) until oral therapy can be initiated | Chloroquine<sup>m</sup>  
Rarely recommended |

**NOTE.** Adapted from Stauffer and Kamat [7], with permission.

- Assume that malaria parasites are sensitive to chloroquine if exposure occurred in Central America, west of the Panama Canal; Mexico; Haiti; the Dominican Republic; or 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 <8 years of age.
- Pediatric dose not approved by the US Food and Drug Administration. Mefloquine should not be given in combination with quinine, quinidine, or halofantrine. It 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, and dizziness. Toxic psychosis and seizures are less common adverse effects.
- May be effective against multidrug-resistant *P. falciparum*, but treatment failures and resistance have been reported. May lengthen PR and corrected QT intervals, and cardiac arrhythmias have been reported. Its use is not recommended when other medications known to prolong PR or corrected QT intervals are being administered or when mefloquine has been used for chemoprophylaxis. Cardiac monitoring is suggested during dosing. Should not be taken within 1 h before and 2 h after a meal.
- Not available in the United States.
- Quinine may have greater antimalarial activity than quinidine. The loading dose should be decreased or omitted for patients who have received quinine or mefloquine. If >48 h of parenteral treatment is required, the quinine dose should be reduced by one-third to one-half.
- Extreme caution must be exercised in administering parenteral chloroquine, because there is a very narrow therapeutic window and overdose may result in death.
areas, they are extremely effective and inexpensive antimalarial drugs. However, they must be used in combination with a long-acting agent to prevent recrudescence of disease.

Chloroquine-sensitive *P. falciparum* is now rarely encountered, except in Haiti. Chloroquine sensitivity may be assumed and treatment considered if the patient was exposed to *P. falciparum* in Central America, west of the Panama Canal; Argentina; Egypt; Haiti; the Dominican Republic; and some Middle Eastern countries.

**Managing complicated *P. falciparum* malaria.** Patients with complicated malaria need immediate parenteral antimalarial drugs and aggressive supportive therapy. Quinidine is the parenteral antimalarial of choice in the United States, and quinine and the artemisinin compounds are available outside the United States. A cardiac monitor should be used and frequent blood pressure measurements should be made when the patient is receiving quinine derivatives. These agents must be administered as a gradual intravenous infusion to avoid acute cardiovascular complications, particularly hypotension. Infusion rates should be reduced if the QT interval is prolonged by >25% from its baseline value. Quinidine is becoming increasingly rare in United States hospital pharmacy formularies but may be acquired directly from the manufacturer, Eli Lilly. If quinidine acquisition is delayed, parenteral clindamycin may be initiated until quinidine is available. Oral therapy is initiated as soon as it can be tolerated by the patient. It should be noted that a second agent (i.e., sulfadoxine-pyrimethamine or doxycycline) must be used in conjunction with quinine, quinidine, or, especially, the artemisinin compounds, because when these agents are used alone, excessive rates of recrudescence are seen.
Table 3. Poor prognostic criteria for patients with severe Plasmodium falciparum malaria.

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Laboratory feature</th>
</tr>
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<tbody>
<tr>
<td>Impaired level of consciousnessa</td>
<td>Hypoglycemiaa (whole-blood glucose level &lt;40 mg/dL)</td>
</tr>
<tr>
<td>Respiratory distressa</td>
<td>Elevated bilirubin levela (total, &gt;2.5 mg/dL)</td>
</tr>
<tr>
<td>Jaundicea</td>
<td>Elevated acidosis (plasma bicarbonate level &lt;15 mmol/L)</td>
</tr>
<tr>
<td>Repeated convulsions</td>
<td>Lactic acidosis (serum lactate level &gt;45 mg/dL)</td>
</tr>
<tr>
<td>Shock</td>
<td>Elevated aminotransferase levels (&gt;3 times normal)</td>
</tr>
<tr>
<td>Laboratory feature</td>
<td>Renal insufficiency (serum creatinine level &gt;3 mg/dL)</td>
</tr>
</tbody>
</table>

* Particularly poor prognostic factor in children (especially the combination of respiratory distress and impaired level of consciousness) [38].

Close monitoring and supportive therapy are imperative for good outcome. Initial hypoglycemia should be treated with a rapid infusion of 25% (for infants and small children) or 50% dextrose. To prevent and monitor for hyperinsulinemic hypoglycemia, administration of a 5% or 10% dextrose solution should be started when treatment with quinine derivatives is initiated, and blood glucose levels should be tested frequently. (Quinine-induced hypoglycemia may develop several days after the beginning of treatment [19].) Hypovolemia and lactic acidosis must be managed with intravenous crystalloids or colloids, and vasopressors and bicarbonate occasionally are necessary. Severe anemia may necessitate blood transfusion. Seizures may be acutely treated with benzodiazepines, and other anticonvulsants may be administered when seizures occur repeatedly or are prolonged. Renal failure may develop; in such a circumstance, adjustment of drug doses is necessary.

Multiple smears with parasite quantification should be done to monitor therapeutic success. Very high levels of parasitemia or failure to respond to treatment may indicate primary drug failure/resistance, and therapy should be adjusted and exchange transfusion considered. Because of the lack of objective data, to what extent exchange transfusion is effective and safe has been debated, and the exact criteria for initiating therapy are unclear. Some authorities have suggested that exchange transfusion may be beneficial for any severely ill patient with parasitemia of >15% or for any patient with parasitemia of 5%–15% who has signs of poor prognosis (table 3) [37, 38]. Clinical trials do not demonstrate efficacy for other ancillary treatments, including anticytokine agents, chelation agents, corticosteroids, mannitol, dextran, heparin, and malaria hyperimmunoglobulin [18, 19]. When managing a severe case of malaria, an experienced infectious diseases or tropical medicine specialist should be consulted, and additional support may be obtained through the Centers for Disease Control and Prevention malaria hotline (770-488-7788).

Treatment of Nonfalciparum Malaria

P. vivax and P. ovale are usually susceptible to chloroquine. Recent exceptions to this rule have been documented in P. vivax from South America and Oceania, particularly New Guinea. In patients for whom the likelihood of chloroquine-resistant P. vivax is high, mefloquine or quinine/quinidine plus doxycycline (for patients >7 years of age) may be used [28, 30]. In patients with P. vivax or P. ovale malaria, the initial treatment regimen should be followed by treatment with primaquine (“radical cure”). Primaquine is effective against the exoerythrocytic liver phase and is administered to prevent relapse, but occasional relapses may still occur, despite administration of appropriate therapy. Glucose-6-dehydrogenase levels should be measured in all patients who receive primaquine before initiation of therapy, because severe hemolytic anemia may occur in patients with a deficiency of this enzyme. For patients with glucose-6-dehydrogenase deficiency, primaquine should not be used, and each subsequent relapse should be treated with chloroquine or an acceptable alternative. Primaquine should not be used to treat newborn infants. Children who acquired malaria transplacentally or via a transfusion do not have hypnozoite forms of malaria and need not be treated with primaquine.

P. malariae is susceptible to chloroquine, which is the drug of choice. This parasite does not have the ability to form a hypnozoite in the liver, and, therefore, radical cure with primaquine is not needed.

CONCLUSION

Malaria parasites continue to infect children around the world. With appropriate attention to the possibility of malaria and appropriate use of laboratory tests, delayed diagnosis can be avoided. As new diagnostic and therapeutic tools and techniques become increasingly available, there is ever-greater potential for avoiding the severe morbidity and mortality associated with malaria. Ultimately, an effective and safe vaccine is needed to prevent the tremendous suffering and premature deaths of millions of children every year that are associated with this disease.

References