CLINICAL MALARIA AND TREATMENT OF MULTIDRUG RESISTANCE FALCIPARUM IN THAILAND

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Received December 9, 1998/Accepted April 27, 1999

Abstract: Clinical manifestations of malaria are nonspecific and range from asymptomatic to severe. The clinical presentations reflect complex interactions between the host, the environment, and the parasites. Signs and symptoms include fever, headache, muscle pain, abdominal pain, anorexia, nausea, vomiting, hepatosplenomegaly, jaundice and dark urine. In mild malaria, these signs and symptoms cannot differentiate malaria from common cold, influenza or other systemic diseases. Fever and malaise in malaria are believed to result from the release of endogenous cytokines [e.g. interleukin 1, 6 and 8 (IL-1, IL-6, IL-8) and tumor necrotic factor-α (TNF-α)] in response to parasite antigens. Other signs and symptoms of malaria are also associated with the rupture of parasitized red cells. In severe malaria, the clinical manifestations included cerebral malaria, pulmonary edema, renal failure, anemia, and jaundice. Signs and symptoms of cerebral malaria are as follows: alteration of consciousness, coma, dysconjugated eyeballs and convulsions. Among fatal cases, 80% died within the first 48 hrs of admission while the rest, death resulted from complications such as acute renal failure, pulmonary edema, bacterial infection, and lactic acidosis. 92% of the survivors had completed recovery. Treatment of multidrug resistant falciparum malaria in Thailand is complicated. New antimalarial drugs have been investigated at the Hospital for Tropical Diseases in the recent years. Artemisinine derivatives such as artesunate, artemether, arteether, dihydroartemisinin are also tested at the Bangkok Hospital for Tropical Diseases. Artesunate and artemether alone with a total dose of 600 to 750 mg produced cure rates of 80 to 95%. Artesunate suppositories have been proved successfully for the treatment of severe malaria. The artemisinin derivatives when used in combination with mefloquine cure rates improved to 95-100%. Dihydroartemisinin alone with a total dose of 480 mg given over 5 days gave a cure rate of 90%. At present, studies with the combination of artemisinin derivatives plus mefloquine in various doses and duration of treatment are being investigated. Until proven otherwise, the drug combinations are still recommended for all adult patients suffering from acute uncomplicated falciparum malaria contracted in multidrug resistant areas.

In severe malaria, the choice of antimalarial chemotherapy depends on the clinical severity, the drug sensitivity of the parasites, and the availability and preparation of the drug. Quinine is widely available drug. Qinghaosu and its derivatives have been used successfully in treating both uncomplicated and severe falciparum malaria. Their effectiveness in eliminating the parasites have been extensively documented, however, the recrudescence rate is rather high (10-30%). In treating severe malaria, early diagnosis and early treatment are vital and the aim is to save patient’s life. Prompt administration of an adequate and effective antimalarial drug is needed once the diagnosis is made. Other symptomatic and supportive treatment includes careful monitoring of fluid intake and urine output, frequent observations for complications with appropriate treatment and good nursing care.

Key words: Malaria, drug resistance, treatment, Thailand

INTRODUCTION

Multi-drug resistant falciparum malaria is a serious problem in Thailand. Therapeutic failures with all available antimalarial drugs are well documented. With this deteriorating situation, new drugs are urgently needed.
needed. The new drugs and drugs in combinations have been studied in Bangkok Hospital for Tropical Diseases since 1988. This paper is an overview of clinical studies on clinical malaria and treatment of multidrug resistance falciparum malaria in Thailand.

Clinical Manifestations

Rupture of intraerythrocytic schizonts coincides with paroxysms of fever and this has led to the traditional categorization of the different types of human malaria. Nowadays, these terms are not recommended, because patterns of fever are variable and some patients die from Plasmodium falciparum even though they never develop periodic fever, particularly in nonimmune patients and during the early stage of illness. Symptoms and signs of malaria are vague including fever, headache, malaise, lassitude, fatigue, muscle pain and loss of appetite. These are not specific for malaria and are similar to the symptoms of influenza or other viral infections. It is essential to take blood samples for examination for malaria parasites.

In severe malaria (Table 1), alteration of consciousness is the most prominent manifestation. The patient usually presents with a history of fever for several days and loss of consciousness, which may be sudden following one or more grandmal seizures. In approximately 50% of patients over 6 years of age, coma follows a convulsion. In young children with cerebral malaria, the history may be very short. Vomiting may also occur; this is important to know because aspiration pneumonia could develop before admission to hospital. In many countries in the tropics, empirical antimalarial or antibacterial treatment and antipyretics have often been given before admission to the hospital. This may explain some reports of patients with cerebral malaria in whom no parasites were demonstrated on a peripheral blood smear. On examination most patients are usually febrile and in unarousable coma. A few patients who have very severe infection have a subnormal temperature. Admission temperature usually exceeds 38.0-39.0°C in most cases and rises above 39.0°C during the first two days of hospitalization. There is no classical pattern of fever in cerebral malaria. Rigors are rare in comatose patients but a sustained high fever, which is resistant to antipyretic treatment, is commonly found. The skin temperature is cool relative to the rectal temperature in hypoglycemic or shocked patients.

Jaundice is common in adult patients and anemia develops rapidly in severe malaria. The chest is usually normal on clinical examination although aspiration pneumonia or pulmonary edema may develop. Changes in respiration can be a warning sign of hypoglycemia, metabolic acidosis, pneumonia, and pulmonary edema, but may occur as a result of high fever alone. Therefore careful examination and proper investigations should be performed in all patients.

Hepatosplenomegaly is common. In Thailand, half of the adults and children over 6 years with cerebral malaria have a palpable liver or spleen. Massive splenomegaly is most unusual in severe malaria. Abdominal pain and tenderness are prominent in some patients. In children, the physical signs are similar to adults except that convulsions are more common, hepatomegaly may be prominent, and anemia is common; jaundice is relatively less frequent.

Retinal hemorrhages occur in 15% of cerebral malaria patients in Thailand. Hemorrhages may occur anywhere in the retina. Some appear similar to Roth’s

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Definition of severe malaria and complicated falciparum malaria</th>
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<tbody>
<tr>
<td>1.</td>
<td>Cerebral malaria</td>
</tr>
<tr>
<td>2.</td>
<td>Severe anemia (Hct&lt;15%)</td>
</tr>
<tr>
<td>3.</td>
<td>Renal failure (no urine or urine output &lt;400 ml in 24 hr, or 12 ml/kg/24 hr after rehydration, or serum creatinine &gt;3 mg/dl)</td>
</tr>
<tr>
<td>4.</td>
<td>Pulmonary edema or adult respiratory distress syndrome</td>
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<td>5.</td>
<td>Hypoglycemia (blood sugar&lt;40 mg/dl)</td>
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<td>6.</td>
<td>Shock (systolic BP&lt;70 mmHg in adult or &lt;50 mmHg in children age 1-5 years)</td>
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<tr>
<td>7.</td>
<td>Spontaneous bleeding and disseminated intravascular coagulation</td>
</tr>
<tr>
<td>8.</td>
<td>Repeated convulsions</td>
</tr>
<tr>
<td>9.</td>
<td>Acidosis (arterial pH&lt;7.25 or plasma HCO₃&lt;15)</td>
</tr>
<tr>
<td>10.</td>
<td>Macroscopic hemoglobinuria</td>
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<tr>
<td>11.</td>
<td>Hyperparasitemia (&gt;5% parasitemia in non-immunes)</td>
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<tr>
<td>12.</td>
<td>Hepatic dysfunction</td>
</tr>
<tr>
<td>13.</td>
<td>Hyperpyrexia (persistence of rectal T&gt;40°C)</td>
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</tbody>
</table>
spots, which are associated with endocarditis. Exudates are unusual and papilledema is rare (less than 1%). The hemorrhages resolve rapidly in survivors and do not interfere with vision after recovery of consciousness. Systemic bleeding due to disseminated intravascular coagulopathy (DIC) is present in a few patients (less than 5%). Abnormal eye movements such as divergence of the eyes or nystagmus are seen occasionally. Pupillary responses to light, and the oculocephalic and oculovestibular reflexes are always normal. Corneal reflexes are usually present. There may be passive resistance to head flexion but other signs of meningeal

Table 2 Clinical trials of oral antimalarial drug either alone or in combination with other anti-malarial drugs
in Bangkok Hospital for Tropical Diseases

<table>
<thead>
<tr>
<th>Reference and drug</th>
<th>Total dose (mg)</th>
<th>Duration (d)</th>
<th>No. of patients</th>
<th>Cure rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Looareesuwan et al., 1992</td>
<td>Artesunate 600</td>
<td>5</td>
<td>40</td>
<td>88</td>
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<tr>
<td></td>
<td>Artesunate 600</td>
<td>5</td>
<td>39</td>
<td>100</td>
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<td></td>
<td>followed by mefloquine 25 mg/kg divided into 2 doses</td>
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<td></td>
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<tr>
<td>Looareesuwan et al., 1993</td>
<td>Artesunate 300</td>
<td>2.5</td>
<td>50</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>follow by mefloquine 15 mg/kg divided into 2 doses</td>
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<tr>
<td>Looareesuwan et al., 1994</td>
<td>Artesunate 300</td>
<td>2.5</td>
<td>55</td>
<td>80</td>
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<td></td>
<td>plus doxycycline 200 mg/d×7 d</td>
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<tr>
<td>Looareesuwan et al., 1997</td>
<td>Artemether 500</td>
<td>5</td>
<td>40</td>
<td>74</td>
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<tr>
<td></td>
<td>Artemether 750</td>
<td>7</td>
<td>58</td>
<td>98</td>
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<td></td>
<td>Artemether 800</td>
<td>1</td>
<td>53</td>
<td>98</td>
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<td></td>
<td>follow by mefloquine 25 mg/kg divided into 2 doses</td>
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<tr>
<td>Looareesuwan et al., 1996a</td>
<td>Dihydroartemisinin 480</td>
<td>7</td>
<td>53</td>
<td>90</td>
</tr>
<tr>
<td>Looareesuwan et al., 1999</td>
<td>CGP 56697</td>
<td>Artemether 320</td>
<td>2</td>
<td>126</td>
</tr>
<tr>
<td></td>
<td>and benfluorexol 1,920</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Looareesuwan et al., 1996c</td>
<td>Atovaquone 9,000</td>
<td>1</td>
<td>25</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>Atovaquone 12,000</td>
<td>3</td>
<td>24</td>
<td>100</td>
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<td></td>
<td>plus proguanil 4,800 mg</td>
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<td></td>
<td>Atovaquone 5,000</td>
<td>5</td>
<td>24</td>
<td>100</td>
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<td></td>
<td>plus proguanil 2,000 mg</td>
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</tr>
<tr>
<td>Looareesuwan et al., 1996b</td>
<td>Pyronaridine 1,200</td>
<td>3</td>
<td>69</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>Pyronaridine 1,800</td>
<td>5</td>
<td>32</td>
<td>88</td>
</tr>
<tr>
<td>Wilairatana et al., 1997</td>
<td>Biguanide-dapsone</td>
<td>Dapsone 200</td>
<td>3</td>
<td>10</td>
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<td></td>
<td>plus proguanil 400</td>
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<tr>
<td></td>
<td>Biguanide-dapsone</td>
<td>Dapsone 200 plus Chlorproguanil 70</td>
<td>3</td>
<td>14</td>
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</tbody>
</table>
irritation are absent. Ankle clonus is present in one third of patients. The abdominal reflexes are almost absent. There is no other clinical evidence of autonomic dysfunction in cerebral malaria. The duration of coma is 48–72 hrs in most adult patients in Thailand. After treatment most (92%) of the survivors have complete recovery.

**Treatment**

1) **Uncomplicated falciparum malaria**

With the emergence of multidrug resistant falciparum malaria in Thailand, new drugs and drugs in combination are urgently needed. The artemisinin derivatives when used in combinations with mefloquine improved cure rates to 95-100% (Looareesuwan et al., 1993). Dihydroartemisinin alone with a total dose of 480 mg given over 5 days gave a cure rate of 90% (Looareesuwan et al., 1996; Wilairatana et al., 1998). Combination of artemether with benflumetol proved safe and effective (cure rate over 90%) in the treatment of acute uncomplicated falciparum malaria (Looareesuwan et al., 1999). Other combinations (artemisinin derivatives combined with doxycycline, mefloquine combined with tetracycline or doxycycline) have also been evaluated with the improvement in cure rates (Table 2) (Looareesuwan et al., 1994).

2) **Severe malaria**

Management of severe malaria bases on the early diagnosis and early treatment with a potent antimalarial drug. Early detection and treatment of complications (convulsions, acute renal failure, pulmonary edema, acidosis, hypoglycaemia, hyperthermia) are essential. The aim of management is to save the patient’s life. The choice of antimalarial chemotherapy depends on the clinical severity, the drug sensitivity of the parasites, and the availability and preparation of the drug.

**Quinine**

Quinine is the most commonly used and available drug in treating falciparum malaria. Recently, its effectiveness has declined when used alone. Quinine resistance is appearing in several parts of the world including Tanzania, Vietnam, and Thailand; however, most of the resistance is at the RI level. Minimal inhibitory concentrations (MIC) of quinine for P. falciparum parasites have risen above 10 mg/l in some areas. In this situation, and in severe malaria, a loading dose of 20 mg of quinine dihydrochloride per kg body weight, and maintenance doses of 10 mg per kg given every 8 hrs, are required. Persistent parasitemia after a loading dose of quinine is not uncommon. It is believed that the MIC of quinine must be maintained for seven days of effect complete cure of P. falciparum infections. Therefore, quinine must be given for at least seven days or longer. In quinine-resistant areas, a second drug such as tetracycline or doxycycline has been added to increase cure rates, which approached 100% in 1986 but declined to 90% in 1991. For children, in whom tetracycline is contraindicated, increasing the dose of quinine to 15 mg/kg in the second half of the treatment period improves the cure rate.

In severe malaria, if the patient has not received quinine or mefloquine in the previous 24 hrs, then an initial loading dose of 20 mg/kg of quinine dihydrochloride salt should be infused over 4 hrs followed by maintenance doses of 10 mg/kg at 8 hrs intervals until the patient can take oral medication, for a total treatment course of 7 days. The initial doses should never be reduced, the maintenance doses should be reduced by one-third if by the third day of treatment there has been no clinical improvement, or if there is established acute renal failure. Hypoglycemia is the most serious and frequent adverse effect of cinchona alkaloids.

**Quinidine**

Quinidine, the diastereomer of quinine, has a lower MIC for P. falciparum in Thailand. It is as effective as or perhaps more effective than quinine for the treatment of falciparum malaria, as shown in open trials of oral quinidine sulfate and parenteral quinidine gluconate in both acute uncomplicated and severe falciparum malaria in Thailand. Quinidine bisulfate and quinidine slow-release formula was tested in uncomplicated falciparum malaria in Thailand in 1983–1984. They proved effective (with the cure rate of 100%), were well tolerated and had few side effects. They should be considered as alternative antimalarial drugs in the treatment of uncomplicated falciparum malaria.

In places where quinine is not available, such as Japan, America or Europe, quinidine may be used in
place of quinine. It is 4 times more effective but also 4 times more cardiotoxic than quinine. The electrocardiogram shows consistent dose-related prolongation of the QTc interval. In severe malaria, an initial loading dose of 15 mg base/kg is given over 4 hrs, followed by 7.5 mg base/kg given over 4 hrs at 8 hrs intervals. Quinine should be substituted when it becomes available to complete a 7 days treatment course. Hypotension is a serious side effect particularly when it is given over a period of less than 4 hrs.

Combination of quinine, quinidine and cinchonidine

In vitro testing against fresh isolates of *P. falciparum* suggested that a combination-containing equal part (1 : 1 : 1) of the three drugs was more potent than the individual drugs. In clinical trials, this combination was studied in uncomplicated falciparum malaria in Thailand. The combination drug was given every 8 hrs in a dose of 11.4 mg base/kg for 7 days. The results revealed that neither the oral nor the intravenous preparations of the three drugs are toxic and that it is effective in the treatment of chloroquine-resistant falciparum malaria. However, the drug is not generally available.

Qinghaosu (artemisinin) derivatives

Qinghaosu is sesquiterpene lactone peroxide extracted from the qinghao plant (*Artemisia annua* L.). It has been used in Chinese traditional medicine for over 2000 years, to treat the chills and fever associated with malaria. The active constituent, artemisinin, was isolated in 1972. Qinghaosu derivatives are highly effective in killing parasites; however, recrudescence rates are high. Attempts have been made to reduce the high recrudescence rates by increasing the dosage, or lengthening the period of drug administration, or using drug combinations. Two derivatives, (artemether and artesunate) are now widely used and have been registered in Thailand. Other qinghaosu derivatives including arteether and artelinic acid, are under development.

Artesunate

Artesunate is formulated either as tablets (50 mg tablet) or as a dry powder of artesunic acid for injection (supplied in 60 mg vial with an ampoule of 1 ml 5% sodium bicarbonate). The powder is dissolved in the 1 ml sodium bicarbonate and then further diluted in 1 ml of normal saline and use immediately as intravenous or intramuscular injection. Artesunate is manufactured by Guilin No. 2 Pharmaceutical Factory, Guangxi, China. It has rapid antimalarial activity with the clearance of over 90% of parasitemias within 24 hrs (Wilairatana *et al.*, 1997). However, recrudescence rates are high, ranging from 10 to 30% depending upon the dose and duration of initial treatment. A recent study in Thailand has shown that oral artesunate at a total dose of 600 mg given over 5 days had a cure rate of 88% (Looareesuwan *et al.*, 1992). However the efficacy increased to 100%, in both acute uncomplicated and recrudescent falciparum malaria infections, when mefloquine 1,250 mg (divided in 2 doses 6 hrs apart) was given following artesunate treatment. If a half dose of artesunate (300 mg) was given over 2.5 days, followed by 750 mg mefloquine, the cure rate reduced to 90% (Looareesuwan *et al.*, 1993, Looareesuwan *et al.*, 1997). Both oral and parenteral preparations of artesunate have been licensed for use in Thailand. In order to reduce the high recrudescence rate, the optimum dose of artesunate in combination with other drugs such as mefloquine or tetracycline or doxycycline is currently being investigated in Thailand.

Artemether

Artemether (60 mg ampoule), manufactured by Kunming Pharmaceutical Factory, Kunming, China, is formulated in peanut oil for intramuscular injection and licensed for use in Thailand. Oral artemether (50 mg tablet or capsule) is undergoing clinical trials. As with artesunate, the parasiticidal effect is rapid, with clearance of over 90% of parasitemias within 24 hrs. Unfortunately, recrudescence rates are also high. Optimum dose of artemether combined with other drugs such as mefloquine, tetracycline or doxycycline is being under studied in Myanmar and Thailand.

Symptomatic treatment

Supportive and symptomatic treatment of malaria are equally important to antimalarial drugs since most patients have headache, nausea, vomiting, diarrhea, high fever and inability to take any food while they are ill. Therefore, rehydration and the use of antipyretic and antiemetic drugs may be necessary. Antipyretics and antiemetics drugs should be administered a few hours before antimalarials are given, in order to reduce the chance of vomiting and to comfort the patients. After antimalarial drug administration, it is advisable to keep patients under observation for an hour or let the patients lie down, to make sure that they have completed the dose and do not vomit. If they vomit within 1 hr, the dose should be repeated.

In severe malaria, especially in cerebral malaria, intensive care of the unconscious patient and treatment
of life-threatening complications such as pulmonary edema, metabolic acidosis, renal failure, hypoglycemia, bacterial sepsis, and aspiration pneumonia are essential (WHO, 1990). Cerebral malaria is an emergency condition, which requires intensive care during the first 48 hrs of admission (Warell, 1997). It has been calculated that nearly 80% of patients die during this period. Other complications or manifestations should be treated as follows:

**Hyperthermia**

Cerebral malaria patients usually deteriorate while they have high fever. Temperatures above 38.5°C are associated with an increased incidence of convulsions, especially in children. Temperatures between 39.5°C and 40°C is associated with delirium, and above 42.0°C with coma. High body temperatures may cause permanent severe neurological damage. In pregnant women with malaria, high fever is associated with fetal distress. In the severely ill patient, cooling blankets, fanning, and tepid sponging are necessary. In the tropics, clinicians often accept the risk of agranulocytosis and use parenteral antipyretics such as dipyrone.

**Acute pulmonary edema**

Although pulmonary edema may develop at any stage of the acute illness, it tends to occur later than the other acute manifestations of malaria. Central venous pressure is a useful measure of hydration. A permeability edema associated with normal pulmonary wedge pressure measurements may develop at any time in the first few days of treatment and is difficult to treat. There is no specific therapy and management should be the same as that for adult respiratory distress syndrome occurring in other conditions. Malaria in pregnancy usually has a high risk of pulmonary edema, particularly after delivery.

**Acute renal failure**

This results from acute tubular necrosis. Some impairment of renal function is common in adults with cerebral malaria and is also associated with classical blackwater fever but only a minority of patients go on to develop established renal failure. Hypercatabolic acute renal failure should be managed by dialysis or conservative treatment if dialysis is not available. Hemodialysis treatment in acute renal failure from malaria does not shorten the course of acute tubular necrosis, which is usually last for 1–3 weeks. Hemodialysis requires 5–10 times during the 1–3 weeks of anuria. Fluid balance should be strictly monitored.

**Hepatic dysfunction**

This is manifested by jaundice, raised serum enzymes, prolonged prothrombin time, decreased serum albumin and lactic acidosis. Bilirubinemia is predominantly of the unconjugated type but some patients show an increase in conjugated bilirubin, indicating hepatocellular damage. Saline enema in these patients is recommended (Wilairatana et al., 1994).

**Hypoglycemia**

Hypoglycemia should be reversed by intravenous dextrose and plasma glucose maintained between 80–120 mg/dl. Frequent monitoring is essential. This condition should be suspected in any patient whose consciousness is deteriorating, who develops convulsions or who has changed respiratory patterns.

**Shock ("algid malaria")**

This is most commonly the result of hypovolemia or complicating sepsis.

**Severe anemia**

Anemia develops very rapidly in cerebral malaria and blood transfusion is often required. Anemia results from a combination of bone marrow suppression and accelerated red cell destruction of both parasitized and unparasitized red cells. Blood should be crossmatched on admission and transfused to maintain the hematocrit over 21%. Fresh blood is preferable as thrombocytopenia and clotting factor depletion may coexist with anemia. Transfusion rates should be slow to avoid volume overload, and it may be necessary to give a potent diuretic such as furosemide intravenously at the same time.

**Metabolic acidosis**

This condition is serious and rapidly fatal. Lactic acidosis and renal impairment both contribute to hydrogen ion retention. Lactic acidosis results from the parasite, increased anaerobic glycolysis and a failure of hepatic gluconeogenesis. Sodium bicarbonate provides temporary correction of acidosis. Dichloroacetate has proved to be safe and to decrease the degree of acidosis. However, it did not reduce the mortality rate in a randomised controlled study in adult patients suffering from other diseases. The drug should be tested in cerebral malaria patients.

**Hyperparasitemia**

In nonimmune patients with severe falciparum malaria, mortality increases with the degree of para-
sitemia. Exchange transfusion may reduce the burden of parasitemia more rapidly than chemotherapy alone and might also remove harmful toxic products e.g. toxins and cytokines (Looareesuwan et al., 1998; Udomsangpetch et al., 1997; Wenisch et al., 1998). This technique replaces blood, plasma, platelets, clotting factors and correct other abnormalities e.g. fluid, electrolytes and acid-base imbalance. Exchange transfusion should be considered in nonimmune patients who have more than 10% parasitemia and who have deteriorated on the conventional chemotherapy and have at least two complications of severe falciparum malaria e.g. cerebral malaria, renal failure, jaundice or acute pulmonary edema. In areas where total exchange transfusion is not possible, partial exchange transfusion with 4-6 units of fresh blood performed manually, alternately venesecting and transfusing the patient is still useful. Monitoring of central venous pressure, vital signs and blood pressure must be done frequently during exchange transfusion.

**Bacterial Infections**

Gram-negative septicemia, aspiration pneumonia, and urinary tract infections may complicate cerebral malaria and should be treated with appropriate antibiotics. Any patient who develops shock at any stage should be investigated because up to 40% of such cases have been found to have positive blood cultures.

**Coagulopathy**

Using sensitive measures, activation of the coagulation cascade be detected in all patients with acute symptomatic malaria, but significant disseminated intravascular coagulopathy occurs in less than 5% of patients with severe disease. Replacement therapy (not heparin) is essential, and in the tropics fresh blood is preferable.

**Prognosis**

Poor prognostic indicators in severe falciparum malaria include deep coma, repeated convulsions with signs of decerebration, high parasitemia (>5% in nonimmunes), peripheral schizontemia, clinical jaundice or more than three-fold elevated serum enzyme concentrations, uremia (creatinine more than 3.0 mg/dl and blood urea nitrogen more than 60 mg/dl after rehydration), metabolic acidosis (elevated plasma and/or cerebrospinal fluid lactate, or arterial blood gas <7.2), leucocytosis (>15,000/μl), retinal hemorrhages and hypoglycemia (clinical hypoglycemia or blood glucose <40 mg/dl).

**Chemoprophylaxis**

1. **General Principles**

   A practical approach to any prophylaxis regimen includes the following concepts:
   - Drugs should begin at least 1 week before entering a malarious area. The drugs must be taken regularly and, for most regimens, continued for at least 4 weeks after leaving the endemic area.
   - No antimalarial regimen is completely effective, even with absolute compliance. Antimalarial chemoprophylactic regimens do not prevent infection: they suppress the infection sufficiently in most cases so that clinical signs and symptoms do not appear. In areas of increasing drug resistance, 'breakthrough' infections will occur more frequently.
   - Chemoprophylaxis should always be combined with personal protective measures such as the use of insecticide impregnated bed nets for sleeping, avoiding peak mosquito biting times, using insect repellents on exposed surfaces, and wearing clothes that minimize exposure.

   Antimalarial prophylaxis by people living in malaria endemic areas remains controversial. Pregnant women are at increased risk for severe malaria and should take antimalarial prophylaxis. Antimalarial prophylaxis in children living in endemic areas has been shown to reduce mortality, but some issues remain unsettled.

   Recommendations for malaria chemoprophylaxis in travelers are complicated by compliance issues and adverse effects. In areas where the risk of infection is low or there are brief exposures in intermediate or high transmission areas, travelers may carry a treatment course of antimalarial drugs ('standby drugs') instead of taking prophylaxis. If they become ill, especially in areas without medical facilities, the treatment is self-administered.

2. **Current Prophylactic Drugs**

   Increasing drug resistance in many parts of the world, especially Southeast Asia and South America, is slowly diminishing the effectiveness of many prophylactic regimens. Knowing the drug resistance patterns of *P. falciparum* in different geographic locations is essential for choosing an appropriate regimen.

   The major chemoprophylactic drugs for falciparum malaria include doxycycline, mefloquine.

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