Management of Malaria: Recent Trends
S. R. Mehta* and S. Das**

ABSTRACT
In the present day scenario of resurgence of infectious diseases, malaria compounded with problems of multi drug resistance, assumes paramount importance. A combination of artemisinine derivatives with other effective anti-malarial drug remains the most effective form of treatment against the falciparum malaria which is most lethal form of disease. Oral chloroquin in the dose of 25 mg base/kg over 48 hours is effective in infections due to P. vivax, P. ovale P. malariae and chloroquine sensitive P. Falciparum. For chloroquine resistant P. vivax and multidrug resistant falciparum malaria, a combination of Quinine with doxycycline or clindamycin for 5-7 days, Quinine with singlt dose sulfadoxine-pyrimethamine combination. Mefloquine with artemeter or artesunate for 3 days, artesunate with doxycycline or clindamycin for 7 days and Otovaquin with proguanil for 3 days have been found to be effective. Primiquin as a hypnozoticide for 5-10 days is mandatory for preventing relapse in cases of P. vivax, P. Ovale and P. malariae.

Death due to complicated malaria can be as high as 75% if case diagnosis is delayed or the patient arrives late. The artemisinine based rectal suppositories can be very effective in home/village setting in patients who can not be given oral anti malarial, though not yet approved for use in our country. In ICU settings, properly administered loading dose of quinine has proved to be effective and safe in almost all therapeutic trials including our study on Indian patients. Freqent blood glucose monitoring is mandatory. Parentral artemisinine with oral mefloquine is an effective alternative to quinine based therapy.

The cerebral malaria management in the ICU setting includes monitoring fluid and electrolyte balance so as to maintain a CVP of 5 cm of water and pulmonary arterial occlusive pressure at less than 15 mm of mercury. In renal failure haemofiltration is ideal. Mefloquine is safe in second and third trimester of pregnancy. Exchange transfusion, haemopheresis and plasmapheresis are new techniques in the treatment of gravely ill patients with PF malaria especially when parasitemia exceeds 10%.

* Maj. Gen. & Senior Consultant Medicine, O/o DGAFM, M Block, DHQ, Min of Defence, New Delhi
** Jt Director, Armed force Medical Services, O/o DGAFM, M Block, DHQ, Min of Defence, New Delhi
INTRODUCTION
Malaria is one of the old diseases of mankind, although under reasonable control at one time, it has re-emerged as a major public health problem in many parts of our country. In recent years, malaria is seen as a cause of slow development in endemic areas. The disease is compounded with problems of parasite resistance, vector resistance and environmental degradation.

Anti-malarial drugs can substantially reduce malaria related morbidity and mortality and improve the situation. Unfortunately the growing problems of drug resistance and its progression to multi-drug resistance and high cost of drugs are serious handicaps in the treatment of malaria. Notwithstanding a properly followed treatment regimen and introduction of new antimalarial drugs from time to time can overcome these problems. Artemisinine based combination therapies (ACT) are the best line of treatment against *falciparum* malaria. Over the past decade, the use of ACT’s having become more and more widespread. ACTs produce very rapid therapeutic response and are well tolerated by people suffering from malaria. Proper management of malaria thus plays a very important role in saving lives, reducing morbidity, breaking the chain of transmission and preventing development of drug resistance. In the following text, I shall be discussing the present day management of malaria.

DIAGNOSIS
It is important to confirm the diagnosis by demonstrating the sexual forms of parasite in well prepared and stained thick as well as thin blood smears (thick smear is for identification of malaria parasite and thin smear for identification of species) as specification of clinical diagnosis is only 20-60% compared to microscopy. A minimum of 100 fields should be examined before a thick slide is declared negative for the parasite. Two slides can be genuinely negative due to cytoadherent property of praticitized RBC. This may be one of the many causes of wide variation in peripheral parasitemia, at times even up to four folds (Fig.1).

**Fluorescence Microscopy**
The sensitivity of staining of parasite DNA with Acridine orange and viewing by ultraviolet microscopy can be as good as with conventional thick film examination. The quantitative Buffy coat (QBC) test is available as a rapid alternative to Romanowsky staining but it requires special training and expensive equipment and diagnosis of species is difficult.
TREATMENT

Basically this depends on the species of malaria, pattern of resistance and severity of infection. Prompt, effective and genuine antimalarials should be administered either orally or parenterally if the patient is unable to swallow and/or tolerate oral drugs. Selection of antimalarials from standard pharmaceutical is essential as counterfeit drugs pose a serious problem in most poor countries where malaria is endemic and the trade in pharmaceuticals is not regulated well. In a survey in Southeast Asia 38% tablets of artesunate contained no drug. All PF cases should be considered as potentially fatal emergencies and proper therapy instituted within minutes of diagnosis as well as the complications must be foreseen and treated. Patient's weight recording is essential to calculate the correct dose of an antimalarial as per salt or base to avoid potentially dangerous situation by over or under dosage. The dosages of selected antimalarials, their base/salt equivalents and duration of therapy are depicted in Table 1.

ORAL THERAPY IN UNCOMPLICATED MALARIA

Oral Chloroquine in total dose of 25 mg base/kg over 48 hours as depicted in Table 1 is effective in most infections due to *P. vivax*, *P. malaria*, *P. ovale* and chloroquine sensitive PF. Chloroquine resistant *P. vivax* is being reported from New Guinea, adjacent islands of Indonesia and some isolated reports from India. These cases can be managed with increasing dosages of chloroquine or

**Immuno Chromatographic Tests for malarial antigen**

These simple to perform, rapid diagnostic dipstick, strip and card tests detect *plasmodium falciparum* histidine rich protein 2 (HRP-2) or parasite lactate dehydrogenase and have opened a new avenue in malaria diagnosis. The sensitivity is almost similar or slightly lower than thick films but these tests do not quantitate the parasitaemia and remain positive for many days after elimination of parasites due to circulating antigen.

**Ancillary investigations**

Rapidly developing anaemia, slight thrombocytopenia and hyperbilirubinemia are usual findings. In complicated *plasmodium falciparum* malaria (PF) hypoglycemia, altered renal and coagulation parameters, hyponatremia, sepsis and metabolic acidosis (specifically lactic acidosis) determine the severity and prognosis. Closed monitoring and timely repeated investigations for these complications have to be carried out for proper management. CSF examination is mandatory in patients with cerebral malaria to rule out treatable encephalapathies. In most cases, CSF is normal but pleocytosis of up to 80 cell/µl and slight elevated total protein (up to 80 mg/dl) may be seen in cases with convulsion. In deteriorating, toxic and hypotensive patients blood culture is essential as bacteremia may coexist due to other severe and life threatening infections as well as a complication of severe PF.

Management of Malaria
### Table 1. Doses & Base/Salt Equivalents & duration of therapy of commonly used antimalarials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage &amp; Duration</th>
<th>Base (mg)</th>
<th>Salt (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine phosphate</td>
<td>10 mg base/kg stat 5 mg/kg at 12, 24 &amp; 48 hours PO</td>
<td>100</td>
<td>161</td>
</tr>
<tr>
<td>Chloroquine sulphate</td>
<td>-do-</td>
<td>100</td>
<td>136</td>
</tr>
<tr>
<td>Chloroquine hydrochloride</td>
<td>-do-</td>
<td>100</td>
<td>123</td>
</tr>
<tr>
<td>Quinine sulphate</td>
<td>10 mg/kg salt 8 hourly 5 to 7 days PO</td>
<td>100</td>
<td>103</td>
</tr>
<tr>
<td>Quinine hydrochloride</td>
<td>-do-</td>
<td>100</td>
<td>105</td>
</tr>
<tr>
<td>Quinidine gluconate</td>
<td>6.25 mg base/kg IV in NS in 2 hours followed by 0.0125/kg/minute #</td>
<td>100</td>
<td>145</td>
</tr>
<tr>
<td>Mefloquine hydrochloride</td>
<td>15 mg base/kg stat followed by second dose 12 hours later 10 mg/kg. - PO</td>
<td>100</td>
<td>110</td>
</tr>
<tr>
<td>Artesunate</td>
<td>2.4 mg / kg IV/IM stat followed By 1.2 mg/ kg at 12, 24 hours and then OD for 3-5 days #</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Artemether</td>
<td>3.2 mg/kg IM- state followed By 1.6 mg/kg OD x 3 days #</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Arteether</td>
<td>150 mg IM OD for 3 days</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sulfadoxine-pyrimethamine</td>
<td>25-1.25 mg/kg (3 tablets single oral dose for adults)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Amodiaquine sulphate</td>
<td>10 mg base/kg OD for 3 days PO</td>
<td>100</td>
<td>130</td>
</tr>
<tr>
<td>Clindamycin hydrochloride</td>
<td>10 to 15 mg base/kg 1M/IV/PO x 8 hour</td>
<td>150</td>
<td>225</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg BD for 7 days PO</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Primaquine phosphate</td>
<td>0.3 mg base/kg for 5 days (maximum dose 15 mg/day). -PO</td>
<td>10</td>
<td>18</td>
</tr>
</tbody>
</table>

# Switch over to oral therapy as early as possible.
NS, Normal saline; IM, Intramuscular; PO, Oral therapy; IV, Intravenous.
subcutaneously every 6 hourly (total dose 25 mg/kg). If the parasite count does not fall below 25% of the pretreatment level in 48 hours, drug resistance is likely and alternative therapy should be instituted without further delay.

Primaquine (15 mg base, adult dose) as a hypnozoiticide for 5-10 days is mandatory for prevention of relapse in infection with \textit{P. vivax} and \textit{P. ovale}. If facilities exist primaquine should be started after ruling out G6PD deficiency. Tafenoquine (Etaquine) a new 8-aminoquinoline which is 10 times more potent than primaquine is likely to be available soon as an alternative to it.

**SEVERE AND COMPLICATED MALARIA**

The mortality from severe malaria can be up to 75% even after institution of proper combination therapy at best possible treatment centre when the patient arrives late and/or the diagnosis is delayed. Home or village based rectal administration of artemisinine derivatives seems a promising approach of treatment for patients who cannot be administered oral antimalarials or are far from intensive care centers. Certain groups of patients (pregnant women and infants) are at particular risk and require special care. To date, no adjunct therapy like steroids, anti-tumor necrosis factor antibodies, pentoxifylline, mannitol and phenobarbitalone for prevention of seizure etc have proved effective; some are even harmful.

**Treatment in intensive care setting**

There is not only a highly significant
Doses and duration of various artemisinin derivatives are shown in Table 1. In situations without IV infusion facilities or when loading dose of quinine is contraindicated, quinine hydrochloride can also be administered by intramuscular route in anterolateral thigh equally divided in each leg after diluting it to 50 to 100 mg/ml.

Suppositories of artemisinin derivatives are also good alternatives for initiation of therapy for severe malaria when intensive care facilities are not available and/or it may take time to reach such a center.

CEREBRAL MALARIA

This should be managed in an intensive care unit with monitoring of fluid and electrolyte balance to maintain the central venous pressure at 5 cm of water and the pulmonary artery occlusive pressure at less than 15 mm Hg. Vomiting, convulsions and aspiration pneumonia relationship between delay in starting chemotherapy and mortality but it also depends as to how soon the therapeutic levels of effective antimalarials are achieved. This can be achieved by initial loading dose of quinine and quinidine. Properly administered loading dose of quinine therapy has been proved very safe and effective in almost all the therapeutic trials, including one in Indian patients.

IV QUININE

20 mg salt/kg as the loading dose, diluted in 10 ml/kg isotonic fluid should be infused over 4 hours, followed 8 hours after the start of loading dose with 10 mg salt/kg infusion over 4 hours, every 8 hourly until patient can swallow. Loading dose is contraindicated only if the patient has taken quinine, quinidine or mefloquine in preceding 48 hours. Though the initial dose should never be reduced but in patients with subsequent renal failure or those who are seriously ill even after 48 hours of intensive parenteral quinine therapy, the subsequent maintenance dose should be reduced by 30 to 50% (Fig.2). Frequent blood glucose measurement is mandatory and all patients on parenteral quinine should receive 5% glucose infusion. The manifestation of hypoglycemia, a frequent finding in these patients, can be confused with features of cerebral malaria. Parenteral artemisinin including loading doses for artemether and artesunate combined with oral mefloquine or pyrimethamine-sulfadoxine is an effective alternative to quinine based therapy for severe PF. The

doses and duration of various artemisinin derivatives are shown in Table 1.

Intravenous infusion facilities not available/not possible

In such situation loading dose as well as subsequent doses of quinine hydrochloride can also be administered by intramuscular route in anterolateral thigh equally divided in each leg after diluting it to 50 to 100 mg/ml. Suppositories of artemisinin derivatives are also good alternatives for initiation of therapy for severe malaria when intensive care facilities are not available and/or it may take time to reach to such a center.

CEREBRAL MALARIA

This should be managed in an intensive care unit with monitoring of fluid and electrolyte balance to maintain the central venous pressure at 5 cm of water and the pulmonary artery occlusive pressure at less than 15 mm Hg. Vomiting, convulsions and aspiration pneumonia
therapy. Adult respiratory distress syndrome is managed with early positive pressure ventilation for noncardiogenic pulmonary edema. Careful monitoring of hepatic and haematological parameters is needed and blood transfusion should be given when haematocrit is rapidly falling or is less than 20%. One of the causes for shock and/or deterioration despite good antimalarials is bacteremia, mainly gram-negative; hence cefazidime/ceftriaxone therapy should be started immediately.

TREATMENT OF PREGNANT WOMEN AND CHILDREN
Chloroquine, quinine, quinidine, clindamycin, azithromycin, and proguanil are safe for pregnant and breast-feeding women. Mefloquine is teratogenic in high doses in animals, hence not approved for use in pregnancy, and should definitely be avoided in the first trimester. Limited short-term studies have suggested that mefloquine is safe in the second and third trimesters. Pyrimethamine-sulfadoxine is probably safe in pregnancy but should be avoided in the third trimester due to risk of kernicterus. The use of artemisinin derivatives in pregnant women can be justified in severe multidrug resistant PF only in second and third trimester. Tetracycline, doxycycline, primaquine and halofantrine are contraindicated in pregnancy.

Chloroquine though safe in children, its parenteral dose should be calculated very accurately as the overdoses (or even correct doses in volume depleted patient) have caused many deaths. Mefloquine represents an efficient treatment for acute
uncomplicated *P. falciparum* malaria in children and is well tolerated even in infants.

**PRESCRIPTIVE AND EMPIRICAL TREATMENT**

In areas with high transmission all fever cases where clinical features strongly suggest malaria-proper first line antimalarials should be administered. In very sick, deteriorating patient with impending organ failure a therapeutic trial with six doses of quinine is fully justifiable even if repeated blood examinations for the parasite are negative. These patients need very close follow up subsequently.

**EXCHANGE TRANSFUSION**

The risk of death from *P. falciparum* is proportional to the density of parasitaemia. Mortality rises as parasitaemia exceeds 2% or 100,000 parasites/ul. With 10% parasitaemia, despite optimal treatment, 15% to 50% of patients still die. Exchange transfusion, haemopheresis and plasmapheresis- the new technique for the treatment of gravely ill patients with PF malaria have the theoretical advantage of rapidly removing parasitized red cells, parasitic toxins and red cell debris replacing them with fresh plasma and unparasitized erythrocytes with normal rheological properties.

The volume of the exchange transfusion may range from as few as four units of whole blood or packed red cells to a full, two- volume exchange (8 to 10 L of blood). Though not yet proven in a randomized trial to enhance survival, these measures should be considered for seriously ill patients with PF parasitaemias exceeding 10%, and for patients with life-threatening coma, respiratory failure, coagulopathy, or fulminant renal failure. The exchange transfusion should be continued until the level of parasitaemia has fallen below 5%.

**THERAPEUTIC MONITORING AND THE PROBLEM OF CARDIOTOXICITY (INCREASED QTc ETC)**

Because facilities for in vitro drug sensitivity testing are unlikely to be available soon, the efficacy of malarial treatment must be measured clinically. After 48 hours of therapy, most patients with uncomplicated, drug-sensitive malaria should show marked clinical improvement, and by 96 hours most should have defervescence. Thick and thin blood smears should be examined every 12 hours until the parasitaemia has fallen below 1%. Parasitaemia that has not declined by at least 75% of the admission value after 48 hours or has not cleared after 7 days of treatment indicates drug resistance and the antimalarial regimen should be changed. Gametocytes, which may appear or persist in the peripheral blood during treatment and follow up do not signify drug resistance or treatment failure.

Most antimalarials (except probably the artemisinin derivatives) are cardiotoxic, hence proper QTc and other cardiac monitoring is needed for all seriously ill cases even in patients without underlying heart disorders. Mefloquine is contraindicated in patients with
arrythmias, organic heart disease and in those with past history of psychiatric disorder.

References


