Malaria in South-east Asia*

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SENIOR SCIENTISTS and physicians working on various aspects of malaria in Southeast Asia met in Bangkok from 18th to 22nd August, 1976 a report of which under the editorship of Tranakchit Harimasuta, H. M. Gilles and A. A. Sandosham has just been printed. The following are extracts which may be of interest and use to our readers.

CURRENT STATUS

Malaria occupied a prominent position in the disease hierarchy in the pre-DDT era in the countries of this region. Many countries started an eradication programme which initially edged out the disease. It has now staged a comeback in some of the countries and in others it is just gaining ground. The increase in population and the need for economic development have led to more and more land being opened up for agriculture with an increase in malaria. These areas are not readily accessible and conditions unsettled; the farmers and their families are in constant movement living in temporary shacks. In these circumstances DDT spraying cannot be carried out with the degree of efficiency needed to assure interruption of malaria transmission.

Even if all houses can be regularly sprayed it is doubtful, for various reasons such as outdoor transmission, constant movement of population, etc., if eradication can be achieved by use of DDT alone. Owing to political instability, lack of funds from curtailment of foreign aid, economic recession, etc., most Southeast Asian countries have been forced to abandon the concept of eradication in favour of control especially in highly malarious areas hoping to reduce malaria incidence to a level where it ceases to be a serious public health problem.

Malaysia is an exception in that an eradication programme was started only in 1967. There is some optimism of greater success here because of politically stable conditions, a Government willing and able to finance the project, an excellent infrastructure of health services for integration, etc.,It remains to be seen.

For most of the countries of the region the best prospects lie in the development of the health infra-structure and in areas relatively free of malaria integration with the general health services. In areas of high endeminity a variety of methods should be deployed to reduce the prevalence of malaria and prevent its spread to clean areas. A mobile team of anti-malaria workers should be available in each district to act speedily on receiving information of an outbreak of malaria in any locality to contain and eliminate its spread.

TREATMENT

The working group advocated the following lines of treatment in Southeast Asia:-

Treatment of vivax malaria

Day 1 – Chloroquine base 900 mg. orally in three divided doses (e.g. 300 mg. four to six hourly)
Day 2 – Chloroquine base 300 mg. (two tablets)
Day 3 – Chloroquine base 300 mg. (two tablets)

plus

Primaquine 15 mg./day for fourteen days

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The course of primaquine can be started simultaneously on Day 1 with the beginning of chloroquine treatment. A weekly 45 mg. dose of Primaquine for eight weeks is a safer regimen in G-6-PD deficient patients whenever this is practical.

Treatment of falciparum malaria

(1) **Uncomplicated disease**

a. Quinine sulphate 650 mg. (salt: 2 tabs.) every 8 hours for three days plus Sulfadoxine 1.5 g. with Pyrimethamine 75 mg. (three tablets Fansidar).

The dose of Fansidar is administered on the first day together with the first dose of quinine. The cure rate of this combination is over 90% and the early control of symptoms provided by quinine is highly desirable. Ideally, this regimen should be given in hospital but in certain circumstances it can be given to out-patients.

b. An acceptable alternative when the above regimen is not feasible logistically or economically is a single dose of 1 gm. sulfadoxine with 50 mg. pyrimethamine (two tablets Fansidar) – cure rate 80 – 90%.

c. Parental therapy should not be given to out-patients.

d. Symptomatic therapy: Standard supportive treatment (e.g. antipyretics) should be given, but it is important to be aware that any immunosuppressive or anti-inflammatory drug (including aspirin) may prolong the duration of parasitaemia.

e. In areas where control or eradication programmes are underway the use of primaquine is advocated as a public health measure (gametocytocidal effect) on the completion of the curative courses (a or b) mentioned above as follows:–

Primaquine 15 mg. daily × 5 days

or

Primaquine 45 mg. single dose

(2) **Complicated or severe disease**

A. **Chemotherapy**

1. Quinine 650 mg. (salt) intravenously in 500 ml. of saline (or any preferred infusion fluid) given over ½ to two hours, repeated 8-hourly until the patient is able to take oral medication.

a. Occasionally a very ill patient may require 2 – 3 days of intravenous quinine; in such a case, quinine 650 mg. (salt) in 500 ml. fluid should be given 8-hourly, administered over a 4-hour period. The daily dose of quinine should not exceed 2.0 gm.

b. Patients must be observed for signs of toxicity or idiosyncrasy, and the dosage reduced accordingly.

c. The dose of quinine in children should not exceed 5 mg/kg/dose.

2. The dose of Fansidar may be given via gastric tube. An intramascular preparation is also available and is an acceptable alternative to the oral form when required.

3. When the patient is able to take medication by mouth, oral therapy should proceed as outlined above. [See (1)a.]

NOTE: The use of intramuscular quinine is not advocated by the group for the following reasons: (a) the injection is painful and in some cases causes sterile abscess, (b) absorption of the drug is relatively poor-blood levels achieved are less than those following oral administration, (c) unless sterility is guaranteed pyogenic abscess and even tetanus occur, particularly when the drug is used outside of hospitals and in private clinics, (d) there is a possibility of injury to the sciatic nerve.

B. **Management of complications**

The management of the patient with complications is as important as chemotherapy which of course is *mandatory* in all cases. The most common severe manifestation of falciparum malaria seen in Southeast Asia are:

i. cerebral malaria
ii. renal failure
iii. haemolysis with severe anemia (mostly in children).
iv. blackwater fever, malarial haemoglobin urea
v. pulmonary oedema

Blackwater fever is rare while disseminated intravascular coagulation is still most controversial. Until the status of DIC in malaria is definitely determined it is *un-*

justified and dangerous to use heparin routinely in the treatment of severe falciparum malaria.

i. **Cerebral malaria:** In addition to the conventional management of convulsions or coma, corticosteroids probably help by reducing cerebral oedema when this is present and possibly by improving vascular permeability and tone. Parasite clearance may be prolonged as with any other anti-inflammatory drugs.

Dexamethasone should be given intravenously, at a dosage of 6 – 8g. m every six hours, until consciousness is regained. If dexamethasone is not available alternative corticosteroid preparations may be used.

N.B. Occasionally in endemic areas of malaria a patient presents in coma; and a presumptive clinical diagnosis of cerebral malaria is made but the blood smear is reported as negative.

In these patients the routine advocated is as follows:

(a) Give the initial dose of parenteral antimalarials as above [(2)A 1a].

(b) Investigate for other possible causes of coma. Lumbar puncture and examination of urine are necessary.

(c) Repeat blood smear every four hours and act accordingly.

It is vital in these cases that one is satisfied with the competence of the reporting laboratory.

ii. **Renal failure:** Many patients with severe falciparum malaria are dehydrated. If a history of diminished urinary output is elicied (less than two cups on the day before admission) and/or physical signs of dehydration are present, the first dose of quinine should be diluted in 1,000 ml. of infusion fluid and given over the period of one hour to two hours.

If evidence of oliguira persists 2,000 ml. of fluid should be given over a period of two hours followed by an intravenous injection of furosamide 80 – 100 mg.

If within the next six hours oliguira persists or anaemia occurs repeat the intravenous infusion of 2,000 ml. as above followed by 100 mg. of furosamide. Steroids may also be given at this stage. If no response occurs after all this, the patient should be dialysed-peritoneal or haemodialysis. If this is not available conservative conventional treatment is given.

iii. **Haemolysis and severe anaemia:** These are among the commonest complications in children. Parasitaemia is not uncommonly scanty and a malarial aetiology has often been based on the following factors:

a. Haematological evidence of haemolysis – e.g. reticulocytosis
b. Normocytic anaemia
c. Presence of malarial pigment (thin film) and/or gametocytes
d. Excellent response to specific antimalarial therapy

The anaemia can be severe enough (2.0 g) to result in heart failure. The management is as follows:

a. Transfusion of packed cells (or whole blood if former not available) to raise haemoglobin to Hb 6 – 7 g. or hematocrit 20%.
b. Conventional treatment of heart failure (if this is present).
c. Steroids may have a place because immunological factors may be involved in the pathogenesis of anaemia.

iv. **Blackwater fever:** This term which is now redundant was introduced many years ago in clinical malariology and at the time it denoted certain specific diagnostic criteria which were as follows:

a. It occurred in areas where malaria was endemic.

b. It occurred in non-immunes, usually in those taking quinine irregularly as a suppressive or using spasmodic inadequate curative treatment.

c. Parasitaemia was scanty or even absent in most cases.

d. An antigen-antibody reaction triggered by quinine was thought to be responsible for the massive haemolysis.

Cases of **malarial haemoglobinuria** are occasionally still seen and the circumstances are usually as follows:

a. The condition occurs in non-immunes usually living in highly endemic areas of malaria.

b. It may be associated with heavy or with light parasitaemia.

c. It has no connection with irregular intake of quinine.

d. Undetermined immunological factors are probably involved.

e. Patients should be G-6-PD normal. When acute haemoglobinuria occurs in *non-immune* G-6-PD deficient patients in malarious areas it is difficult to be certain whether the aetiology is due to the enzyme-deficiency or whether it is malarial in origin. A useful but not absolute differential criterion is the Coomb's test. This is negative in cases of drug induced G-6-PD deficiency but usually (though not invariably) positive in malarial haemoglobinuria. When acute haemoglobinuria occurs in semi-immunes in malarious areas it is almost certainly due to G-6-PD deficiency with drug sensitivity and should not be labelled either blackwater fever or "a malarial haemoglobinuria".

Malarial haemoglobinuria: This is now a very rare complication in Southeast Asia. The majority of cases of acute haemoglobinuria are usually associated with G-6-PD deficiency and not with malaria.

The treatment is similar to that advocated for haemolysis or severe anaemia above. The use of quinine and Fansidar are not likely to increase the haemolysis and in any case are mandatory in the presence of parasitaemia.

v. **Pulmonary oedema:** This condition is usually fatal within 24 hours of onset. It often occurs when parasitaemia is resolving and may be confused with "uraemic lung".

a. A careful balance must be attempted between early rehydration in severe malaria and limitation of fluids to prevent pulmonary oedema.

b. Conventional management of pulmonary. oedema as seen in other conditions, eg. congestive heart failure.

c. Steroids may be a useful adjunct.

CHEMOPROPHYLAXIS

a. **Chloroquine** is effective against vivax malaria and against falciparum malaria in areas where the parasite is still sensitive.
Dose: 300 mg. base weekly.

b. In chloroquine-resistant areas, a few regimens are available but is emphasized that at present none are completely satisfactory nor conclusively proven effective in all areas especially in *non-immunes*. Possibilities include the following:
1. Proguanil 200 mg + Dapsone 25 mg daily. (Black 1973)
2. Dapsone 100 mg + Pyrimethamine 12.5 mg (Maloprim) once weekly.
3. Sulfadoxine 1 g + Pyrimethamine 50 mg (Fansidar: 2 tabs) once fortnightly.
4. Sulfadoxine 1.5 g + Pyrimethamine 75 mg (Fansidar: 3 tabs) once monthly.
5. Proguanil 200 mg daily: less effective than (1). (Black 1973).

Fansidar is best reserved for therapy, but may be considered in certain situations, e.g.

a. Labour forces in endemic areas during the months of high transmission.

b. Short term traveller (three months or less).

c. Other carefully selected and supervised groups, e.g. Students engaged in field work.