DGAFMS MEMORANDUM - 158

MALARIA PROPHYLAXIS AND TREATMENT

General considerations

1. Malaria - a preventable vector-borne systemic disease – continues to be a major cause of morbidity and mortality worldwide. Global resurgence of malaria has been due to the spread of resistance of parasite to chloroquine and other affordable antimalarials along with resistance of the vector to insecticides. Almost all deaths in malaria are due to *P falciparum* infection which causes severe illness with multi-organ dysfunction. Delay in diagnosis of falciparum infection and initiation of appropriate therapy for the same allows an uncomplicated attack to become severe or complicated one leading to high mortality. It is imperative for all medical officers to be aware of symptoms and signs of severe illness so as to start treatment at the earliest and prevent severe or fatal complications, especially in high-risk groups such as young children and pregnant women.

2. In view of the limited drug options available for treatment and prophylaxis of malaria, priority should be given to prevention, early diagnosis and treatment, and close monitoring of drug resistance. With increasing deployment of our troops overseas, awareness of the global risk of malaria and drug resistance patterns is also necessary. Four important principles of malaria protection are:

(a) Awareness in troops and families of the risk of malaria

(b) Avoidance of mosquito bite

(c) Early diagnosis and treatment

(d) Chemoprophylaxis where indicated

Awareness in troops and families of the risk of malaria

3. All troops and families staying/moving in malarious areas should be made aware of the risk of malaria infection, how they can best protect themselves and urgently seek medical advice if they get a fever. Troops going for night operations or camping particularly in forested areas may be at highest risk. Pregnant women and young children should take extra precautions against malaria and avoid travel to highly malarious areas if possible. The following points should be highlighted:

(a) Initial symptoms of malaria may often be mild, and malaria should be suspected if, one week after entry into an endemic area or upto 2 months after leaving an endemic area, they suffer unexplained fever with or without other symptoms like headache, muscular aching, weakness, vomiting, diarrhoea and cough. Prompt medical advice should be sought in such situations.

(b) Malaria can be fatal if treatment is delayed beyond 24 hours. Medical help should be sought promptly if a febrile illness occurs. A thick and thin blood smear should be made and examined for malarial parasite in all fever cases.

(c) Antimalarial drugs for self-treatment should be taken only when prompt medical help is not available. Affected persons should complete the treatment course as advised by the medical officer.

Avoidance of mosquito bite

4. Troops and families should be told that protection from mosquito bite is their FIRST LINE OF DEFENCE against malaria. Practical measures for such protection are as follows:-

(a) Remaining indoors, if possible, in a well-constructed and well-maintained building with effective screens over doors and windows at times when malaria mosquitoes are biting (between dusk and dawn); if no screens are available, windows and doors should be closed at sunset.

(b) Wearing full - sleeved clothing, trousers and footwear with socks after sunset. Application of insect repellant to exposed skin between dusk and dawn when malaria mosquitoes commonly bite. Repeated applications may be required every 3-4 hours, especially in hot and humid climates.

(c) Use of mosquito - nets with edges tucked in under the mattress, and ensuring that the net is not torn and that there are no mosquitoes inside. Where available, use of pyrethroid-treated mosquito - nets may provide better personal protection.

(d) Spraying of indoor sleeping areas with anti-mosquito sprays, or use of mosquito coils, vaporizing mats or liquid vaporizers in the bedroom at night.

Early diagnosis and treatment

5. The medical officers and troops should be aware that **no prophylactic regimen against malaria gives complete protection in malarious areas.** Falciparum malaria, which can be fatal, must always be suspected if fever, with or without other symptoms, develops at any time between one week after the first possible exposure to malaria and two months (or even later in rare cases) after the last possible exposure. *The most*

important factors that determine the survival of patients with falciparum malaria are prompt recognition of the disease/complications and urgent appropriate treatment. The aims of management are to avoid mild malaria from becoming severe or complicated (untreated mild falciparum malaria can progress to severe disease in a few hours, specially in children), prevent death/sequelae, limit duration of disease, prevent its transmission and minimize drug resistance. The symptoms of falciparum malaria may not be easy to recognize. It is important, therefore, that the possibility of malaria is considered in all cases of unexplained fever that starts a week after arrival in or upto two months after departure from an endemic area.

Uncomplicated malaria

6. The clinical features of uncomplicated malaria are common to all four species. The symptoms of malaria preceding fever are non-specific and include headache, bodyaches, and occasionally abdominal pain and diarrhoea. Diagnosis may be missed with serious consequences for the following reasons:

(a) fever may be absent
(b) fever may not be associated with rigors
(c) fever may not have tertian/quartan pattern

A young child may have irritability, refusal to eat, and vomiting. On examination, fever may be the only sign, and some patients may have palpable liver and spleen. This clinical picture may be misdiagnosed as influenza in non-endemic or low endemic areas.

Severe malaria

7. Death from vivax, ovale, or malariae infection is rare and may be due to fatal hemorrhage following a ruptured spleen (either traumatic or spontaneous). However, falciparum malaria can progress to severe disease rapidly and is a potentially lethal infection. The patient may present with confusion or drowsiness with extreme prostration. In addition, the following severe manifestations may develop singly, or more commonly, in combination in the same patient :-

(a) Cerebral malaria
(b) Severe anaemia
(c) Generalized convulsions
(d) Hypoglycaemia
(e) Acute renal failure
(f) Acute pulmonary oedema
(g) Circulatory collapse (“algid malaria”)
(h) Jaundice
(j) Abnormal bleeding
(k) Haemoglobinuria
(l) Metabolic acidosis with respiratory distress
(m) High grade fever

In high transmission areas, the risk of developing severe falciparum malaria is greatest among young children and visitors from non-endemic areas (like soldiers on deployment). In non transmission and low transmission areas, the risk is greatest in people returning from areas having falciparum transmission. Only early detection and prompt treatment of severe malaria can reduce its overall morbidity and mortality.

Diagnosis of malaria

8. Diagnosis of malaria can be clinical and/or parasitological.

(a) *Clinical Diagnosis:* Signs and symptoms that can be used for early recognition of severe malaria at periphery are non-specific and could be due to either (i) severe malaria, or (ii) another severe febrile disease, or (iii) severe malaria with severe bacterial infection. In children, signs and symptoms of severe febrile disease are: history of fever plus one of these - prostration, altered consciousness, lethargy or coma; breathing difficulty; severe anaemia; inability to drink; persistent vomiting. For adults, in addition dark and/or reduced urine output may be present. Clinical diagnosis has low diagnostic sensitivity and its criteria vary from area to area depending on many local factors. It may miss some malaria cases with likely serious consequences whereas some others without the disease receive the antimalarial drugs with risks of side-effects and selection of resistant parasite strains. However, in both endemic and non-endemic areas, a high index of suspicion with geographical and movement history indicative of exposure is important. A possibility of induced malaria (through blood transfusion or use of contaminated needles) should also be kept in mind. Severe malaria can mimic many other diseases common in malarious countries such as typhoid, dengue, scrub typhus, leptospirosis, meningitis, haemorrhagic fevers, viral encephalitis, influenza and gastroenteritis. In pregnant women, sepsis from genito-urinary system or breast is an important differential diagnosis. In children, convulsions due to malaria must be differentiated from febrile convulsions.

Diagnosis of malaria should be included in the differential diagnosis of any individual with a febrile illness who has had potential exposure to malaria within past 2 to 3 years. In areas with high risk of malaria, young children and pregnant women having fever and/or history of fever within past 4 days or clinically detectable anaemia should be treated for malaria. In older children, adult males, and non-pregnant women, presence of fever or history of fever in the past 4 days is the only criterion for treating as malaria. However, one should not miss other conditions mentioned above in differential diagnosis.

(b) Parasitological diagnosis:

(i) BASIC MICROSCOPY. Where possible a definite species diagnosis should be obtained by microscopic examination of blood smear. Examining thick and thin films of peripheral blood 12 hourly for 36 to 48 hours for malarial parasite is sensitive and cheap, differentiates between the malarial species, determines parasite density and can also diagnose many other conditions. Thick smear can detect low-density parasitaemia, and thin smears help in

identifying the parasite species. In areas with high transmission, asymptomatic parasite carriers may be common from immunity developing due to repeated malarial infections. Malarial disease may exist despite a negative microscopy result particularly in severe falciparum infection, or in patients already on antimalarials. Unless required on clinical grounds, treatment for uncomplicated malaria should not be given as long as blood slides are negative. In general, heavy parasitaemia, specially in non-immune persons (residents of non-endemic or low endemic areas) means severe disease **but one must remember that fatal malaria can occur with low parasitaemia.**

(ii) QUANTIFIED BUFFY COAT (QBC). This technique for detection of parasite has high sensitivity and specificity but is prohibitively expensive.

(iii) NEWER TESTS. Human infection can be picked up by two "dipstick" tests on fingerprick blood sample. One detects the malarial antigen, Plasmodium falciparum Histidine Rich Protein II (PFHRP II). The test is less suitable for diagnosis of new infections or identifying treatment failures as PFHRP II antigenaemia persists after effective treatment. The other test detecting parasitic specific LDH (pLDH) does not have these drawbacks and has the added advantage of detecting infections with other species also. Polymerase Chain Reaction (PCR) test for the parasite is the most sensitive method. However, the newer tests are not yet available for routine use.

9. Parasitaemia should be monitored every 4 to 6 hours for first 2 to 3 days of treatment. More than 20% of mature parasites with visible pigment mean bad prognosis. Malarial pigment in neutrophils indicates malaria, specially in anaemic children and in severe malaria with absent or low parasitaemia. Finding more than 5% of such leucocytes worsens the prognosis. Other laboratory findings in severe malaria are anaemia, thrombocytopaenia and peripheral leucocytosis (not necessarily indicating bacterial infection). Blood urea, serum creatinine, bilirubin, and aminotranferases may be raised. Electrolyte and acid-base disturbances may be present.

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Treatment

10. The treatment of malaria may achieve clinical cure (clearance of signs and symptoms but not necessarily of parasites) or radical cure (clearance of parasites along with clearance of symptoms and signs). Primaquine is given in falciparum malaria as a gametocytocide to reduce reservoir of infection, whereas, in vivax and ovale malaria it eliminates tissue phase preventing relapses. Chloroquine achieves radical cure in *P malariae* infection as it does not have hepatic stage.

UNCOMPLICATED MALARIA.

11. Chloroquine resistant *P vivax* is not a public health problem so far. **However, *P falciparum* has become resistant to chloroquine globally except in parts of Central America.** In such situations, other suitable drugs may be considered. Mefloquine can be

given to chloroquine/other anti-malarial resistant uncomplicated falciparum cases only on prescription of medical practitioner with laboratory report showing asexual stage of falciparum and not gametocytes or other species. The treatment schedules advocated by the National Anti-Malaria Programme (NAMP) are as follows:

Low Risk Areas

(a) **Presumptive treatment:** single dose of chloroquine base @ 10 mg/kg body weight to all fever cases. (Available chloroquine phosphate tablet of 250 mg contains 150 mg of chloroquine base. Syrup chloroquine phosphate available each 5 ml contains chloroquine phosphate equivalent to 50 mg base).

(b) **Radical treatment on confirmation:**

(i) ***P vivax :*** In addition to the presumptive treatment as at (a) above, under *Low Risk Areas,* chloroquine 10 mg/kg body weight & primaquine 0.25 mg/kg body weight on day 1, followed by primaquine* *0*.25 mg/kg body weight daily for next 4 days (total 5 days). (Primaquine is available as primaquine phosphate tablet of 7.5 mg)

(ii) ***P falciparum : :*** In addition to the presumptive treatment as at (a) above, under *Low Risk Areas,* Chloroquine base 10 mg/kg body weight & primaquine* 0.75 mg/kg body weight stat.

Primaquine is contraindicated in pregnancy, infants and G6PD deficiency.

High Risk Areas

(a) **Presumptive treatment**

Day 1 chloroquine base 10 mg/kg body weight with primaquine* 0.75 mg/kg body weight. Day 2 chloroquine base 10 mg/kg body weight; and on Day 3 chloroquine base 5 mg/kg body weight.

(b) **Radical treatment on confirmation:**

(i) Chloroquine sensitive *P falciparum* areas

(aa) ***P vivax:*** In addition to presumptive treatment as as (a) above under '*High Risk Areas'*, primaquine* 0.25 mg/kg for five days (Relapse seen in *P vivax* and *P ovale* infections is defined as re-appearance of asexual parasitaemia after elimination by drugs. It can result in the patient who has not had adequate radical treatment)

(ab) ***P falciparum:*** No further treatment is required after presumptive treatment as at (a) above under '*High risk areas.*'

(ii) Chloroquine resistant *P falciparum* areas: In addition to presumptive treatment as at (a) above under '*High Risk Areas'* Sulfadoxine 25 mg/kg body weight plus pyrimethamine 1.25 mg/kg body weight on day 1, followed by primaquine* 0.75 mg/kg body weight next day. (Available tablet of sulfadoxine/pyrimethamine contains 500 mg of sulfadoxine and 25 mg of pyrimethamine.

***(Primaquine is contraindicated in pregnancy, infants and G6PD deficiency).**

Pregnancy

Presumptive treatment : Chloroquine 10 mg base/kg body weight. (For other details see under 'Malaria in Pregnancy' and 'Chemoprophylaxis' later.)

Definition of high-risk areas.

12. The criteria for high-risk areas as per NAMP include one or more of the following: -

(a) Recorded deaths due to malaria with *P falciparum infection* (on clinical diagnosis or microscopic confirmation) during the transmission period with evidence of locally acquired infection in an endemic area during any of the last three years.

(b) Slide positivity rate (SPR) is to be used for identification of high-risk areas as follows:

(i) doubling of SPR during the last three years provided the SPR in second or third year reaches 4% or more.

(ii) Where SPR does not show doubling trend as above but the average SPR of the last three years is 5% or more.

(c) *P falciparum* proportion is 30% or more provided the SPR is 3% or more during any of the last three years.

(d) An area having a focus of chloroquine resistant *P falciparum.* A chloroquine resistant area will be characterized by detection of more then 25% of RII and RIII level cases in a minimum sample of 30 cases.

(e) Tropical aggregation of labour in project areas.

(f) New settlements in endemic/receptive areas and vulnerable areas.

In the armed forces context, newly inducted troops in endemic/receptive areas will lead to a high-risk situation.

SEVERE MALARIA

13. *General management.* The patient should be admitted in the ICU. He should be weighed (for calculation of dose of drugs) and nursed on his side with frequent suctioning. Rapid clinical assessment including fundus examination (to rule out papilloedema before lumbar puncture) should be done. He should be given intensive care with initiation of treatment on clinical grounds after making both thick and thin blood films. Antimalarial drugs should be given by intravenous (IV) route, or if IV infusion is not possible, intramuscular (IM) drugs or suppository formulations of artemisinin or its derivatives may be used (if available). Start oral treatment when patient can swallow and retain tablets. Maintain fluid and electrolyte/acid base balance, and monitor frequently for hypoglycaemia. Look for other treatable causes of coma and exclude or cover for bacterial meningitis. Look for oliguria/black urine (haemoglobuniria) which may indicate acute renal failure. Monitor core temperature, respiratory rate, BP and level of consciousness (using Glasgow Coma Scale) regularly to identify hypoglycaemia, metabolic acidosis, pulmonary oedema and early shock. High fever should be managed by tepid sponging and fanning, and paracetamol if required. Start empirical antibiotics if necessary. Monitor therapeutic response – both clinical and parasitological – by regular observation and blood films 4 to 6 hourly for 48 hours. Avoid drugs like aspirin and corticosteroids. Good nursing care has an important role in management of the patient. Specialized care is possible in centers with requisite facilities.

14. *Specific management:* Clinically grave cases or those with heavy parasitaemia are medical emergencies demanding immediate treatment and meticulous care. As per NAMP capsule and tablet forms of artemisinin derivates are not recommended for use in the country so as to prevent misuse of this group of drugs. Artemisinin derivatives are not recommended in pregnancy and infants at present in India. Halofantrine is not recommended due to its erratic absorption, toxicity associated even with therapeutic doses and cross-resistance with mefloquine. Chloroquine resistance is now virtually global and it is therefore advisable to treat all severe malaria cases with quinine or where appropriate, an artemisinin derivative. Loading dose of antimalarials is recommended to ensure adequate therapeutic concentrations promptly. Combination therapy with antimalarial drugs is advised to prevent development of resistance with monotherapy. The regimens detailed below are general guidelines and may require variation in individual cases. A medical officer diagnosing a case of cerebral malaria on clinical or microscopic grounds must ensure immediate evacuation of patient (if fit for the same) to the nearest service hospital having a medical specialist. If patient cannot reach the medical specialist within one hour, the MO should initiate the management of the case (as detailed below) promptly and transfer the case to the nearest service hospital as advised above. The MO should transfer other severe malaria cases also immediately to the nearest service hospital as advised.

(a) Chloroquine sensitive malaria: In view of widespread chloroquine resistance, chloroquine - based regimens should be used with extreme caution and close monitoring

of the patient against any deterioration in his condition. **When parasite sensitivity is doubtful or not known, it is advisable to use the regimes meant for chloroquine resistant malaria. As per NAMP in severe and complicated falciparum malaria (clinically or microscopically confirmed) IV quinine the drug of choice irrespective of chloroquine resistance of the area.** Parenteral chloroquine may be given if quinine or parenteral artimisinin derivatives are not available, and is replaced by them when available. The regimes for chloroquine sensitive malaria are:

Chloroquine 10 mg base/kg in a pint of 5% glucose or normal saline as IV infusion given over 8 hours followed by 15 mg base/kg given over next 24 hours*.

OR

Chloroquine 5 mg base/kg in a pint of 5% glucose or normal saline as IV infusion over 6 hours every 6 hours for a total of 5 doses (i.e., 25 mg base/kg continuously over 30 hours)*.

OR

If IV infusion not possible, chloroquine 3.5 mg base/kg IM or SC every 6 hours. Total dose to be given 25 mg base/kg*.

*(*Change to oral route when patient can swallow and retain the tablets Parenteral administration of chloroquine is more hazardous than parenteral administration of quinine.)*

(b) Chloroquine resistant malaria or sensitivity not known:

(i) Quinine. *For adults*: 20 mg quinine dihydrochloride* salt/kg body weight (loading dose) in a pint of 5% glucose solution by IV infusion over 4 hours. (Alternatively loading dose can be given as 7 mg quinine dihydrochloride /kg in 5% glucose solution as IV infusion over 30 minutes followed immediately by 10 mg quinine dihydrochloride/kg in a pint of 5% glucose solution by IV infusion over 4 hours). Then, 8 hours after the start of loading dose, give maintenance dose of quinine dihydrochlororide 10 mg/kg in a pint of 5% glucose solution as IV infusion over 4 hours. Repeat this maintenance dose every 8 hours calculated from the beginning of the previous infusion. When the patient can swallow, give quinine tablets 10 mg salt/kg 8 hourly to complete a 7 day course of treatment, **or** a single dose of 25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine (maximum 1500 mg sulfadoxine and 75 mg pyrimethamine).

For children: loading dose of quinine as above (i.e., 20 mg/kg body weight) to be given diluted in 5% glucose solution, the volume of 5% glucose solution used for dilution being 10 ml/kg body weight. Then, 12 hours after the start of the loading dose maintenance dose of quinine salt 10 mg/kg body weight diluted in 5% glucose solution

(as before) by IV infusion over 2 hours. Repeat this maintenance dose every 12 hours calculated from the beginning of the previous infusion. When the patient can swallow give quinine tablets 10 mg salt/kg 8 hourly to complete a 7 day course of treatment, **or** a single dose of 25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine.
(**Quinine is available as Inj quinine dihydrochloride 2 ml ampoule containing 600 mg of the salt. Oral preparation available is quinine sulfate tablet of 300 mg)*

Note : 1. If IV infusion is not possible, quinine dihydrochloride can be given in the same dosages by IM injection after dilution in normal saline to a concentration of 60 to 100 mg salt per ml in the anterior thigh (not in the buttock as absorption is erratic and incomplete). The dose of quinine should be divided between two sites – half the dose in each anterior thigh.

2. A loading dose of quinine should not be used if the patient has received quinine, quinidine, or mefloquine within the preceding 12 hours.

3. **Quinine should be combined with** tetracycline 4 mg/kg 4 times daily for 7 days **or** doxycycline 3 mg/kg once daily for 7 days (except in children less than 8 years and pregnant women) **or** clindamycin 10 mg/kg twice a day for 7 days (can be used in children and pregnancy)

4. Loading dose of quinine can be given safely even to patients with renal or hepatic dysfunction and children.

5. If there is no clinical improvement after 48 hours of parenteral therapy, dose of quinine should be reduced by one-third to one-half (i.e. 5 to 7 mg quinine dihydrochloride/kg). Total daily dose of IV quinine in patients will be as follows:-

(a)Adults: First day of treatment - 30 to 40 mg salt/kg body weight. Second day – 30 mg salt/kg. Third and subsequent days – 15 to 21 mg/kg.

(b)Children: First day of treatement – 30 to 40 mg salt/kg body weight. Second day – 20 mg salt/kg. Third and subsequent days 10-14 mg/kg.

6. Intravenous infusion of quinine is usually not required for more than four to five days.

7. Patients on quinine or quinidine should be monitored by ECG for any QTc or QRS prolongation and any dysrrhythmia. Where facilities exist, cardiac monitoring should be done.

OR

(ii) Artemisinin (Qinghaosu) derivatives : Artemisinin is available as capsules or suppositories, artemether and arteether as IM injections and artesunate as tablets, IM/IV injection (supplied with an ampoule of 5% sodium bicarbonate)
Artesunate 2 mg/kg (loading dose) IV followed by 1.0 mg/kg at 12 and 24 hours; then 1.0 mg/kg daily for 4 days. [The preparation available, Artesunic acid 60 mg/ampoule is dissolved in 0.6 ml of 5% sodium bicarbonate diluted to 3 to 5 ml with 5% glucose

solution and given immediately by IV bolus ("push") injection]. When the patient can swallow, the daily dose can be given orally..

OR

Artemether 3.2 mg/kg (loading dose) IM followed by 1.6 mg/kg daily for 5 days. When the patient is able to swallow, the daily dose can be given orally.

OR

Arteether 150 mg IM daily for 3 days in adults only.

Note: 1. Artemisinin derivatives must be followed by administration of oral antimalarial drugs for e.g. mefloquine 25 mg/kg in two divided doses 8 to 24 hours apart to avoid late recrudescence. Mefloquine resistant strains are often cross-resistant to quinine.

2. Artemisinin derivatives are now considered as treatment of choice for quinine resistant falciparum infection and are advised to be used only in areas with multidrug resistant falciparum imfection.

(iii) Quinidine: As a last resort, if none of the above drugs is available, quinidine may be used under cardiac monitoring.

15. If within 48 to 72 hours of treatment, patient does not become afebrile or show signs of clinical improvement, consider (a) inadequate drug level because of inappropriate treatment or poor absorption, (b) high grade drug resistance, or (c) development of complications (hypoglycaemia, renal failure, splenic rupture, gram negative sepsis, and aspiration pneumonia).

Management of important complications

16. In all cases, an appropriate parenteral antimalarial drug should be started immediately as above and complications managed appropriately as below:

(a) Cerebral malaria: It is defined as unrousable coma not attributable to any other cause in a patient with falciparum malaria. The usual mode of presentation is fever with disturbed sensorium. Atypical presentations are known such as afebrile state, disorientation, mental confusion without depressed sensorium, chorea or tremors, focal neurological deficits like mono – or hemiplegia and acute personality changes. Hepatosplenomegaly, convulsions (may be due to infection, fever, hypoglycaemia or electrolyte imbalance), retinal hemorrhages, fixed jaw closure and tooth grinding (bruxism) are common but neck rigidity and photophobia are absent. Papilloedema is rare. Commonest neurological picture in adults is one of symmetrical upper motor neurone lesion with absent abdominal reflexes. Decerebrate (arms and legs extended)

and decorticate (arms flexed and legs extended) rigidity may occur. CSF usually under normal pressure, shows less than 10 leucocytes per microlitre, and slightly increased protein. CT scan brain is usually normal. Exclude other treatable causes of coma e.g. hypoglycaemia, bacterial meningoencephalitis). Institute naso-gastric aspiration of gastric contents, institute condom drainage or insert a urethral catheter as required. Convulsions can be controlled with Inj. diazepam (0.15 mg/kg IV, maximum 10 mg for adults), or injection paraldehyde (0.1 ml/kg IM). Paraldehyde is preferably given from a glass syringe though plastic syringe may be used, provided the injection is given immediately after loading the syringe. Corticosteroids, other anti-inflammatory agents, cerebral de-congestants (urea, mannnitol), low molecular weight dextran, heparin, and desferrioxamine are now considered either useless or dangerous and should not be given. In some cases neurological deficit may persist.

(b) Acute renal failure: It is mostly seen in adults and is usually reversible. It manifests as oliguria and eventually anuria with rise in blood urea and serum creatinine due to acute tubular necrosis. Hypovolemia should be excluded by observing jugular venous pressure or postural hypotension. Cautious fluid challenge with normal saline is given. If patient remains oliguric after adequate rehydration, peritoneal or hemodialysis is indicated.

(c) Circulatory collapse ("algid malaria"): Patients have systolic BP less than 80 mmHg (less than 50 mm Hg in children), cold clammy cyanotic skin and rapid feeble pulse. Complicating gram negative septicaemia, pulmonary oedema, metabolic acidosis, massive gastrointestinal hemorrhage and ruptured spleen may also produce the same picture and need specific management. Dehydration contributes to hypotension. Possibility of infection in lungs, urinary tract, meninges, and IV lines should be kept in mind. Hypovolemia should be corrected with fresh blood or plasma If these are not available, give normal saline. Central venous pressure should be monitored. Broad spectrum anti-microbial cover should be given after sending for blood culture. Fluid and electrolyte balance should be maintained.

(d) Malarial haemoglobinuria ("Blackwater fever"): Haemoglobinuria associated with malaria is uncommon. It usually presents in adults as severe disease with anaemia and renal failure. Screened fresh blood should be transfused avoiding both hypovolumia and fluid overload. Peritoneal or hemodialysis may be required if acute renal failure develops.

(e) Severe anaemia: It is particularly common in young children and pregnant women. If haematocrit falls below 20% or Hb is less than 7 g/dL, whole blood (preferably fresh) or packed cells should be transfused after due screening. Small IV dose of furosemide may be given to avoid circulatory overload.

(f) Abnormal bleeding and DIC: Patient shows bleeding gums, epistaxis, petechiae, and subconjunctival hemorrhages. Haematemesis, melena, and

thrombocytopaenia may occur. Patient should be given fresh blood, clotting factors, or platelets (as required), and Vit K 10 mg slow IV.

(g) Pulmonary Oedema: This may occur in an improving patient several days after chemotherapy has been started. Acute Respiratory Distress Syndrome (ARDS), features develop, first indication being increase in respiratory rate. Iatrogenic pulmonary oedema may occur due to fluid overload. Resultant hypoxia may cause convulsions, worsening of sensorium and rapid death. Treatment of pulmonary oedema due to severe malaria includes propping up the patient, and giving high concentration of oxygen (including mechanical ventilation if required). If pulmonary oedema is due to overhydration, stop all IV fluids, give diuretic, and carry out haemofiltration immediately (if available).

(h) Hypoglycaemia: This is an important and sometimes even recurrent manifestation of falciparum malaria related to severe disease (specially in young children), quinine-induced hyperinsulinaemia or pregnancy (on admission or following quinine treatment). Diagnosis may be overlooked as clinical features of hypoglcaemia are the same as that of severe malaria. Biochemical testing may confirm hypoglycaemia. If it is suspected or detected, 50 ml of 50% glucose (in children, 1 ml/kg), should be given IV after dilution in equal volume of any infusion fluid and given over a period of 5 minutes and followed by IV 5% or 10% glucose infusion. Continuous IV infusion of 5% or 10% glucose solution may be given routinely as a preventive measure against hypoglycaemia in all severe malaria cases.

(i) Aspiration pneumonia: Unconscious patients with convulsions, vomiting and persistent hyperventilation should be evaluated for aspiration pneumonia and managed accordingly.

(e) **Hyperparasitaemia:** Patient should be given parenteral antimalarial therapy even if he or she can take them by mouth. If parasitaemia is more than 10%, consider exchange transfusion .

17. Poor prognostic indicators are (a) Clinical – age < 3 years, deep coma, convulsions, decerebrate or decorticate rigidity, circulatory collapse, acidosis, papilloedema and retinal hemorrhages, and (b) Laboratory – more than 5% parasitaemia, peripheral schizontaemia, polymorphonuclear leucocytosis, mature pigmented parasites more than 20%, PCV < 15%, Hb < 5 g/dL, blood sugar < 40 mg/dL, blood urea > 60 mg% and serum creatinine > 3 mg%.

<u>Common errors in diagnosis and management</u>

18. *Errors in diagnosis*

(a) Failure to elicit history of exposure (movement/travel history)

(b) Failure to think of malaria in a patient with typical or atypical illness
(c) Misjudgment of severity
(d) Failure to make a thick blood film in all cases of fever, faulty blood smear or its inadequate exasmination
(e) Missing *P falciparum* in mixed infections.
(f) Missing hypoglycaemia in a case of severe malaria
(g) Missing other associated infections
(h) Misdiagnosis (i.e., influenza, typhoid, viral encephalitis, hepatitis, scrub typhus)
(i) Failure to recognize respiratory distress (metabolic acidosis or ARDS)

Errors in management
(a) Failure to elicit history of recent antimalarial treatment
(b) Delay in starting antimalarial treatment
(c) Use of inappropriate treatment (use of chloroquine in areas of its resistance, unjustified withholding of an antimalarial, incorrect dose/route of antimalarials and incorrect cessation of treatment, failure to prevent cumulative effects of drugs, continuation of therapy beyond recommended duration, failure to review antimalarial treatment in a patient whose condition is deteriorating, use of unproven and potentially dangerous ancillary treatment).

(d) Inadequate nursing care
(e) Failure to identify/treat metabolic acidosis
(f) Unnecessary endotracheal intubation
(g) Unduly delayed endotracheal intubation
(h) Failure to control convulsions
(i) Failure to recognize minor ('subtle') convulsions
(j) Failure to recognize and treat severe anemia
(k) Delay in considering obstetrical intervention in late pregnancy
(l) Failure to recognize and manage pulmonary oedema
(m) Delay in starting peritoneal dialysis/haemodialysis
(n) Failure to pass nasogastric tube to prevent aspiration pneumonia
(o) Failure to give antibiotic cover for bacterial meningitis if lumbar puncture is delayed
(p) Giving quinine by i.v. bolus ('push')

Malaria in pregnancy

19. Malaria in pregnancy requires prompt treatment as it is more severe, is associated with increased risk of maternal death, abortion, neonatal death, still birth, premature delivery and low birth weight. Cerebral oedema, hypoglycaemia, pulmonary oedema and other forms of severe malaria are more common. Pregnant women with malaria have higher mortality than non-pregnant patients. Timely obstetric intervention should be sought if required. In pregnancy, chloroquine, proguanil, quinine, and quinidine can be given safely. Mefloquine and artemisinin derivatives may be used in second and third

trimester; artemisinin derivatives may be used even in first trimester in severe malaria if other drugs are not available. Sulfadoxine/pyrimethamine may also be used with discretion in second and third trimester. Primaquine, tetracycline, doxycycline and halofantrine are contraindicated both during pregnancy and breast feeding.

Malaria in children

20. Common and most important complications of falciparum infection in children are cerebral malaria, severe anaemia, respiratory distress, and hypoglycaemia. Compared to adults, severe malaria cases in children have short history and duration of illness but more pretreatment hypoglycaemia, neurological sequelae, acidosis, and convulsions. Jaundice, renal failure, pulmonary oedema, and bleeding/clotting disturbances are rare. Routine lumbar puncture in children with severe malaria is controversial but the child should be covered for bacterial meningitis. Management of severe malaria in children is otherwise similar to that in adults. For convulsions, IV diazepam 0.3 mg/kg as a slow bolus over 2 minutes or paraldehyde 0.1 ml/kg IM is given . Earliest feature of cerebral malaria in children is usually fever followed by failure to eat or drink. Unless coma persists for more than one hour after a febrile convulsion, child should not be classified as cerebral malaria. Extreme opisthotonus may occur in some children leading to mistaken diagnosis of tetanus or meningitis. Dextrose normal saline given continuously prevents hypoglycaemia which may be recurrent and is commonly overlooked in children.

Malaria with HIV infection

21. HIV positive patients have greater symptomless parasitaemia, and higher mortality than HIV negative patients. HIV positive pregnant women have an increased risk of falciparum malaria early in pregnancy with greater parasitaemia and higher post-natal mortality. HIV replication is accelerated by the occurrence of malaria leading to higher HIV RNA levels.

Chemoprophylaxis

22. Chemoprophylaxis, applicable for troops in certain specified areas only, is supplementary to personal protective measures, provision of insecticide cover and antilarval measures. It should be carried out UNDER STRICT SUPERVISION, and should be regular and un-interrupted to prevent develop of drug resistance in the parasite. It is also essential that troops continue the prophylaxis while on leave or away from the unit. The drugs available for chemoprophylaxis are chloroquine, proguanil, mefloquine and doxycyline. Increasing parasite drug resistance and drug – specific side – effects make rational guidelines for chemoprophylaxis more and more difficult to compile. There is no ideal drug for chemoprophylaxis. The following schedules for chemoprophylaxis are advocated by the National Anti-Malaria Programme in India :

(a) Chloroquin sensitive areas: Loading dose of chloroquine 10 mg base/kg body weight a week before arriving in endemic area followed by 5 mg base/kg body weight of chloroquine at weekly intervals. Prophylaxis should be continued for 4 weeks

after leaving the endemic area and may be terminated with one dose of chloroquine 10 mg base/kg body weight. Primaquine 0.25 mg/kg body weight is given daily for 5 days.

(b) Chloroquine resistant areas: Same as in (a) above with addition of proguanil 100 mg daily (for adults).

(c) Pregnancy : Chemoprophylaxis should commence at the end of first trimester of pregnancy and should continue till one month after delivery or one month after leaving the malarious area, as applicable. The chloroquine dosage for chemoprophylaxis is same as at (a) above. Primaquine should not be given in pregnancy.

23. Drug allergy and contraindications for the drug(s) used should be ruled out before initiation of prophylaxis. Drugs should be taken with unfailing regularity for the duration of the stay in the area of malaria risk, and continued for 4 weeks after leaving the area, since parasites may still emerge from the hepatic stage during this period. Drugs should be taken with food and swallowed with plenty of water.

24. Adverse reactions attributed to malaria chemoprophylaxis are common. Most of these are minor (mild nausea, occasional vomiting or loose stools), do not affect normal activities and should not prompt discontinuation of prophylaxis. Some antimalarial drugs can cause serious side-effects in which case the individual should stop taking the drug and seek medical advice.

25. Severe adverse reactions during prophylaxis with amodiaquine, sulfadoxine – pyrimethamine have led to their deletion from the list of drugs recommended by WHO for prophylaxis. Other drugs like halofantrine, quinine and artemisinin derivatives are also not recommended for chemoprophylaxis.

Special situations – overseas deployments & multi-drug resistant malaria

26. The above schedules for chemoprophylaxis and treatment apply within the national boundary. However, our troops are exposed to the risk of malaria globally due to deployments in various missions abroad. The armed forces medical services may also be involved in providing medical care to the local population. This may also help reduce the reservoir of infection in the local population near our military units. It is very difficult to frame chemoprophylaxis and treatment guidelines which will have universal applicability due to frequently changing drug resistance patterns besides the varying risks in different continents. It is, therefore, advisable to obtain the latest information on these aspects, pertaining to the area of deployment before initiating any chemoprophylaxis.

27. Where the risk of malaria is generally low and seasonal, falciparum malaria is absent or sensitive to chloroquine, there is no indication for prophylaxis. If it is felt that there is substantial risk, in such areas the drug of choice for chemoprophylaxis is chloroquine; with slightly greater risk, the drug for chemoprophylaxis is chloroquine alone, or a combination of chloroquine and proguanil; the second choice for prophylaxis is mefloquine.

28. In areas of Thailand near the borders with Cambodia and Myanmar, *P falciparum* does not respond to treatment with chloroquine or sulfadoxine – pyrimethamine, and sensitivity to quinine is reduced. Treatment failures of over 50% with mefloquine are also being reported. A similar situation is reported from western Cambodia. In these situations, chemoprophylaxis with doxycycline is recommended along with rigorous use of personal protective measures.

29. The national authorities in Thailand recommend a combination of mefloquine plus artesunate or artemether as the first-line treatment in areas of highly mefloquine – resistant malaria. When these drugs are not available, infections with *P falciparum* acquired on the Thailand/Cambodia and Thailand/Myanmar borders may be treated with a total dose of 25 mg/kg mefloquine, given as 15 mg/kg initially followed by 10 mg/kg 6 – 8 hours later, or with oral quinine, 10 mg/kg of body weight every 8 hours for 7 days, in combination with either tetracycline or doxycycline .

30. Table 1 depicts the various current drug regimens for chemoprophylaxis in various parts of the world.

Table 1. Drug regimens for chemoprophylaxis

Chloroquine: The recommended prophylactic regimen is **5 mg base/kg weekly.** The following table is based on the administration of the commonly used tablets containing either 100 mg or 150 mg base.

Weight(kg)	Age(years)	Number of tablets/week	
		100 mg base	150 mg base
5 – 6	< 4 months	0. 25	0.25
7 – 10	4 – 11 months	0.5	0.5
11 – 14	1 – 2	0.75	0.5
15 – 18	3 – 4	1	0.75
19 – 24	5 –7	1.25	1
25 – 35	8 – 10	2	1
36 – 50	11 – 13	2.5	2
50+	14+	3	2

Proguanil (Paludrine): The recommended prophylactic regimen is **3 mg/kg daily** in combination with chloroquine in chloroquine resistant areas. The following table applies to tablets containing 100 mg proguanil hydrochloride.

Weight (kg)	Age (years)	Number of tablets/day
5 – 8	< 8months	0.25
9 – 16	8 months – 3 years	0.5
17 – 24	4 – 7	0.75
25 – 35	8 – 10	1
36 – 50	11 – 13	1.5
50+	14+	2

Table 1 (contd)

Mefloquine : The following regimens relate to the commonly used tablet containing 250 mg base to be taken for prophylaxis at a **single weekly dose of 5 mg/kg.** Mefloquine should not be given to people with history of epilepsy or psychiatric disorders and those involved in tasks requiring fine co-ordination and spatial discrimination (air crews, deep-sea divers). Vaccination with live bacterial vaccines such as oral live typhoid vaccine should be completed at least 3 days before first prophylactic dose of mefloquine.

Weight (kg)	Age (years)	Number of tablets/week
< 5	< 3 months	Not recommended
5 – 6	3 months	0.25
7 – 8	4 – 7 months	0.25
9 – 12	8 – 23 months	0.25
13 – 16	2 – 3	0.33
17 – 24	4 – 7	0.5
25 – 35	8 – 10	0.75
36 – 50	11 – 13	1
50+	14+	1

Doxycycline: The prophylactic dose is **1.5 mg salt/kg daily**, given as tablets or capsules containing 100 mg doxycycline salt as hyclate or hydrochloride. Doxycycline is mainly recommended for high risk areas where resistance to mefloquine exists. It is also an alternative in high risk areas with high levels of chloroquine resistance for persons unable to tolerate mefloquine.

Weight (kg)	Age (years)	Number of tablets/day
< 25	< 8	Contraindicated
25 – 35	8 – 10	0.5
36 – 50	11 – 13	0.75
50+	14+	1

Note: Proguanil and doxycycline are begun a day before travel to malarious area and continued daily upto 4 week after leaving the area

31. Depending on the advice of local/ international health agencies, the medical authorities may lay down in advance the instructions for management of fever cases occurring in spite of adequate chemoprophylaxis in troops located in small isolated detachments distant from expert medical care,

Monitoring of drug resistance.

32. The primary objective of monitoring drug resistance is to evaluate the efficacy of the recommended treatment options for malaria at the local level with particular emphasis on falciparum malaria. The most suitable method to achieve this objective is monitoring the therapeutic efficacy of antimalarial drugs which has been recently modified by WHO to replace the standard *in vivo* test. Other levels of monitoring exist, including *in vitro* susceptibility testing of parasites and the study of genetic markers of resistance, both of which are very useful for specific research purposes.

Monitoring of therapeutic efficacy.

33. In 1994, WHO set up a new system for monitoring the therapeutic efficacy of antimalarial drugs used for the treatment of uncomplicated falciparum malaria, based on clinical evaluation of selected malaria patients, using a limited number of follow-up examinations. A detailed protocol was developed in 1996 for areas with intense transmission, specially for children under 5 years (unpublished document WHO/MAL/96.1077; available on request from WHO)

34. Between complete sensitivity and complete resistance, there is a gradation in the response of *P falciparum* to anti-malarials ranging from a loss of effect demonstrable only by occasional recrudescence (re-appearance of detectable asexual parasitaemia resulting from persistence of the asexual erythrocytic stage at an undetectable level) to a level of resistance at which the drug apparently has no effect on severe infections. There is thus a spectrum of drug response. The responsiveness of the parasite to the drug is classified as follows:

(a) S (sensitive): - The parasite is accepted to be sensitive if asexual parasitaemia is completely cleared within 7 days of initiation of treatment without subsequent recrudescence. In order to determine whether such recrudescence has occurred or not, blood slides are examined upto a period of 28 days i.e., 1, 2, 3, 4, 5, 6, 7, 10, 14, 17, 21, 24 and 28 days.
(b) R I (resistance at level I): - Asexual parasitaemia clears up as in sensitive but is followed by recrudescence. Recrudescence may be either early i.e., parasitaemia becoming patent again about the 7^{th} day of the initiation of treatment or delayed when parasitaemia becomes manifest after 14 days.

(c) R II (resistance at level 2):- There is marked reduction of asexual parasitaemia, upto 25% or less of the pretreatment level during the first 48 hours of the treatment, but there is no clearance of parasitaemia.
(d) R III (resistance at level 3):- Asexual parasitaemia is reduced by less than 75% during first 48 hours. In some cases parasitaemia may continue to rise without a preliminary reduction. Resistance at R III level may exist when count on day 2 markedly exceeds the count on day 0. In such cases, the trial should be discontinued and the patient given alternative effective drugs.

Note: Limitations of this classification should be kept in mind while evaluating the data based on it.

Procedure for Extended Field Test

35. The patient is weighed. One dose of chloroquine is given on three successive days according to the following schedule:-

Day 0 : 1st dose – 10 mg/kg body weight
Day 1 : 2nd dose – 10 mg/kg body weight
Day 3 : 3rd dose – 5 mg/kg body weight

36. A total of 1.5 gm of base for a 60 kg adult is given. At the time of each drug administration, precautions must be taken to ensure that the drug is swallowed and retained. Drug should not be taken on empty stomach. Severely ill patients should be excluded from the trial. Those with mixed infections should also be excluded. All the time, the clinical condition of the patient takes precedence over the conduct of the test. If the patient is severely ill or if the parasite count is very high, drugs like quinine must be administered in areas of suspected chloroquine resistance.

37. The subject of the test should be observed daily for 28 days. On the first day (day of drug administration), duplicate thick and thin blood films should be made immediately before the first dose and repeated daily. Parasite counts should be made and record kept on a form as per Appendix "A". A thick film is considered negative when the examination of 100 fields does not reveal any asexual parasite. Urine should be collected prior to the drug administration on day 0 and at least once on day 1 or day 2. Urinary excretion of the drug should be determined by the test described in Appendix "B" and "C".

In vitro test

38. A small sample of venous blood is collected in a sterile silicone coated syringe and transferred immediately to a sterile flask containing glass beads. Blood is defibrinated by rotating the flask for 5 minutes, 1 ml aliquots of blood are then placed into screw-capped flat-bottomed glass vials that contains 5 mg of glucose and either no drug (control) or the drug in various amounts. The blood containing vials are then placed in water bath at 38-40° C for a period of 24 hours. After incubation the vials are gently

shaken to resuspend the cells and thick films are prepared. These are stained for 20 minutes by Giemsa stain.

39. This test is based on the principle that maturation of the parasite is inhibited by 4-aminoquinolones. The extent of inhibition can be assessed by comparing the degree of maturation in control samples with that observed in samples containing the drug. The percentage of ring forms that mature to normal looking schizonts containing more than 2 nuclei provides a useful end -point for quantitative assessment of maturation. The number of schizonts per 100 asexual parasites is thus determined for control samples and for samples containing the drug. The values of test samples are divided by the values of the control samples and the results are expressed as a percentage.

38. This in-vitro test can be applied where a hospital laboratory is located nearby and facilities are available. WHO has devised a micro in-vitro test employing a drop of blood. There may not be a close correlation between in-vitro and in-vivo test. In such cases in-vivo test demands consideration.

39. The extended field test and the in-vitro test can also be carried out in asymptomatic carriers of plasmodia but the assessment cannot be dependable if carriers with less than 1000 trophozoites per cmm of blood are screened. As a working guide the tests must be carried out in at least 30 subjects.

40. The specialists in all the three disciplines of medicine, preventive medicine, and pathology must work in close collaboration for investigation, treatment and follow up of the drug resistant cases and the collection of relevant epidemiological data.

APPENDIX 'A'

INDIVIDUAL RESULTS OF EXTENDED FIELD TEST FOR STRAIN SENSITIVITY TO A STANDARD DOSE OF CHLOROQUINE IN FALCIPARUM MALARIA

Name…… Number……

Age……Sex……..….. Weight (kg)……..

Locality……Date of first administration of drug (day 0)…….…….

Particulars of drug……..

Brand and origin…….

Dose of base per tablet…….

	Parasites		Drug dose (mg base)	Urine test	Remarks*
Day	Species	Count@/ per cu mm			
1					
0					
1					
2					
3					
4					
5					
6					
7					
.					
.					
#.					
.					
28					

Note:

@The method of counting parasites (e.g. per 100 fields, per 100 leucocytes, or per 1000 erythrocytes) should be stated.

* including record of temperature

#The blood examination after the first week should be carried out at least twice a week and the findings recorded similarly.

APPENDIX 'B'

WILSON AND EDESON'S TURBIDITY TEST FOR DETECTION OF CHLOROQUINE IN URINE

Reagents :

Mercuric chloride ($HgCl_2$)	- 6.8 G	
Potassium iodide (KI)	- 24.9 G	[Mayor Tanret's Reagent]
Distilled water	- 500 ml	

Method:

Five drops of Mayer Tanret's Reagent are added to 5 ml of fresh clear urine. A white turbidity appears which disappears on heating and reappears as the urine cools down. If albumin is present, turbidity increases on heating. The albumin should be removed by boiling and subsequent filtration. The sensitivity of the test is about 0.4 to 1.0 mg per 100 ml. The test becomes positive within 12 hours after the administration of a single dose of 600 mg of chloroquine base and remains positive for 5-6 days.

APPENDIX ‘C’

DILL – GLAZKO EOSIN COLOUR TEST FOR DETECTION OF CHLOROQUINE IN URINE

Reagent:

50 ml of eosin (yellow) are weighed and transferred to a small glass-stoppered separatory funnel. 100 ml of chloroform (reagent grade) and 1.0 ml of 1 N hydrochloric acid are added and mixture shaken by hand for a few minutes until the chloroform assumes a light yellow colour. The chloroform layer is allowed to separate and is transferred to a brown glass stoppered bottle for future use.

Method:

10 drops of Dill-Glazko reagent (vide supra) are added to 2.0 ml of urine in a test tube. Contents are mixed by vigorous shaking for a few moments. A colour change from yellowish to violet-red in the precipitated chloroform layer indicates presence of chloroquine in urine.

This test is fully reliable only for a period of 48 hours after the administration of the drug. This test is useful when used with urine that cannot be made clear enough even after filtration to apply the turbidity test of Wilson and Edeson (Appendix ‘B’).

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