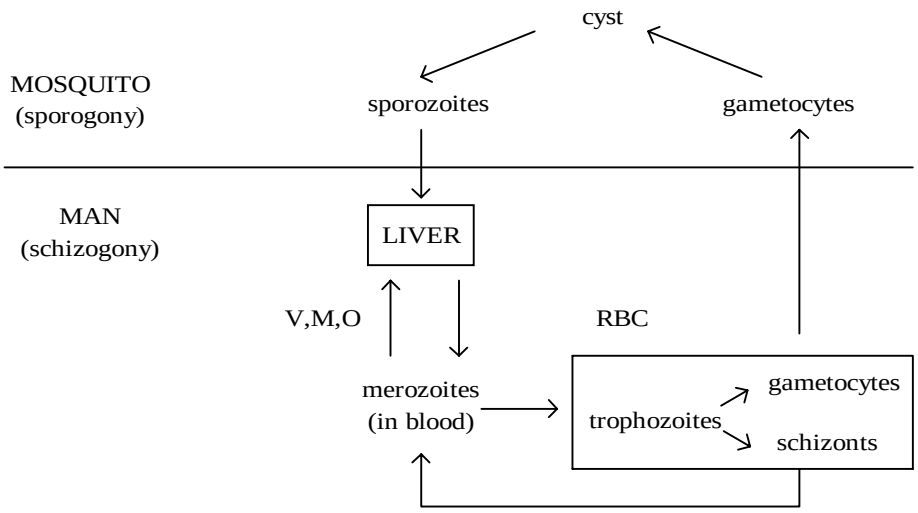
MALARIA - SUMMARY

Note: In view of the significant problems posed by chloroquine resistant malaria and the serious side effects of quinine treatment the Health Department has decided to change the standard management protocols. A single dose of Fansidar is added to the 3-day course of chloroquine or infant Camoquin (amodiaquine) for the treatment of uncomplicated malaria (Treatment A). A 7-day course of Artemisinin derivatives (artemether IMI and oral artesunate) with a single dose of Fansidar on the 3rd day of treatment is used for the treatment of severe malaria (Treatment B) and of treatment failure malaria (Treatment C). The use of a single gameticidal dose of primaquine has been abandoned. Since it will take time for the introduction of the new protocols, both the old and the new are given here. Doctors must be familiar with both.

SUMMARY OF LIFE CYCLE OF MALARIA



SUMMARY OF ANTIMALARIAL DRUGS

	Resistance	Liver phase	Schizonto-cidal	Gameto-cidal	Causal proph.
Schizontocides					
4AQ (chloroq, amod)	F, V	No	Yes	Not F	No
Quinine	F	No	Yes	Not F	No
Fansidar	F, V	Weak	Yes	No	Yes
Proguanil (Paludrine)	F, V, M, O	No	Weak	No	Yes
Pyrimethamine (Daraprim)	F, V, M, O	No	Weak	No	Yes
Artemisinin + derivatives	?Nil	No	Yes	?	?
Mefloquine	?	No	Yes	No	Yes
Exoerythrocytic (liver)					
8AQ (primaquine)	No	Yes	Weak	Yes	Yes

F = falciparum, V = vivax, M = malariae, O = ovale. 4AQ, 8AQ = 4 and 8 aminoquinoline

SUMMARY OF TREATMENT OF MALARIA

Children with malaria are diagnosed into one of three groups:

Uncomplicated malaria

Children who are febrile but who are not very sick (very sick being defined as a child who has an indication for admission - see Paediatric Rules, p.286). These children are treated with chloroquine or infant Camoquin and a single dose of Fansidar, as per Treatment A1 (new regimen) or as per Treatment A2 (old regimen).

Note: A single dose of primaquine has been given as a gametocidal as part of routine treatment of malaria in Papua New Guinea. There is no convincing evidence that it is effective in reducing malaria transmission and it has been discontinued.

Severe malaria

Children who are febrile and who are very sick - ie have any of the indications for admission (see Paediatric Rules, p.286) or who are unconscious or convulsing (the latter situation loosely categorised as 'cerebral malaria' - though the WHO definition specifies the presence of impaired consciousness for more than one hour after the fit). These children are treated with Treatment B1 or B2. They are also usually treated for meningitis with chloramphenicol until this diagnosis has been excluded by a CSF examination.

Note: In the old regimen, parenteral quinine is followed by three days of oral quinine - plus Fansidar and primaquine. Thus, total duration of quinine therapy is not 3 days - but may be 4-7 days. This aspect of treatment has often been overlooked.

Treatment failure malaria

Children who have not responded to a correctly administered, swallowed and appropriate treatment course, or who are deteriorating after starting treatment for uncomplicated malaria, or who have another attack of malaria within one month of completing a standard course of chloroquine or infant Camoquin. Treat these children as per Treatment C1 or C2.

SUMMARY OF THE IMMEDIATE MANAGEMENT OF THE COMPLICATIONS OF SEVERE MALARIA

1. Weigh the child.
2. Check the airway and lie the child on the side.
3. Do a blood slide, FBE, dextrostix, U+E, culture and cross match.
4. Start 10% dextrose IV.
5. Start treatment as per Treatment B1 or B2.
6. Assess hydration clinically, urine SG and output (catheter if necessary).
7. Decide fluid requirements (coma regimen in STB).
8. If the temperature is over 40 ºC, give paracetamol, tepid sponge, fan.
9. Check the fundi: if there is no papilloedema, do an LP.
10. Give anticonvulsants, antibiotics and vitamin K if necessary.
11. Give a blood transfusion if the Hb is 6 g/dl or less.

Coma - maintain the airway, nurse on the side, turn 2 hourly, exclude other causes of coma (meningitis, hypoglycaemia) and avoid harmful treatments (steroids, heparin).

Hyperpyrexia - give paracetamol, tepid sponge and fan.

Convulsions - maintain the airway, give paraldehyde and then phenobarbitone, check the blood glucose (do a dextrostix).

Severe anaemia (Hb 6 g/dl or less) - give a blood transfusion and frusemide.

Haemoglobinuria - alkalinize the urine if this is very severe.

Acute pulmonary oedema - prop up at 45º, and give oxygen and frusemide, stop IV fluids (this complication is less common in children than in adults).

Acute renal failure - exclude dehydration, give 5 ml/kg saline over 20 min. If there is still no urine, give frusemide 2 mg/kg, then 4 mg/kg, then 8 mg/kg IV at hourly intervals. If there is still no urine, give dopamine 2.5 microgram/kg/min via central line for 6 hours. If the child is still oliguric, start peritoneal dialysis.

Spontaneous bleeding - transfuse fresh whole blood, and give vitamin K.

Metabolic acidosis - exclude hypoglycaemia, hypovolaemia and sepsis.

MALARIA - TREATMENT AND COMPLICATIONS

REMEMBER: fever in children is frequently NOT due to malaria, even in highly malarious areas. Treat for malaria, but look for other causes of fever.

Daily parasite density counts may be useful in severe malaria, or if you suspect resistance. Note that amodiaquine and chloroquine do not kill the gametocytes of P falciparum - only the persistence of P falciparum trophozoites shows resistance. Distinction must be made between trophozoites and gametocytes. Record the daily trophozoite count in the patient's notes.

UNCOMPLICATED MALARIA TREATMENT

Treatment A1 (New)

Give amodiaquine (Infant Camoquin) or chloroquine (Nivaquine) tablets daily for 3 days. Give a single dose of Fansidar on day 1 of treatment.

Uncomplicated malaria: Treatment Chart A1 (New)

Weight (kg)	Amodiaquine 100 mg tab Daily for 3 days	Chloroquine 150 mg tab Daily for 3 days	Fansidar Single dose
3 - 5.9	½ tab	¼ tab	¼ tab
6 - 9.9	1 tab	½ tab	½ tab
10 - 14.9	1½ tab	1 tab	1 tab
15 - 18.9	2 tab	1 tab	1 tab
19 - 27.9	-	1½ tab	1½ tab
28 - 36.9	-	2 tab	2 tab
37 - 49.9	-	3 tab	2½ tab

Treatment A2 (Previous but without the single dose of primaquine))

Give amodiaquine (Infant Camoquin) or chloroquine (Nivaquine) tablets orally for 3 days.

Uncomplicated malaria: Treatment Chart A2 (Previous)

Weight (kg)	Amodiaquine 100 mg tab Daily for 3 days	Chloroquine 150 mg tab Daily for 3 days
3 - 5.9	½ tab	¼ tab
6 - 9.9	1 tab	½ tab
10 - 14.9	1½ tab	1 tab
15 - 18.9	2 tab	1 tab
19 - 27.9	-	1½ tab
28 - 36.9	-	2 tab
37 - 49.9	-	3 tab

SEVERE (COMPLICATED) MALARIA - INCLUDING CEREBRAL MALARIA

Take a blood slide and do a lumbar puncture and dextrostix. Give oxygen. Put up a 4.3% dextrose in 0.18% normal saline (dextrose-saline) drip. If the patient is fitting, stop the fit with paraldehyde or diazepam, and commence treatment with phenobarbitone (loading dose IMI 15 mg/kg as per STB). If the patient is hypoglycaemic, give intravenous 10% dextrose 5 ml/kg.

- Cloudy CSF (or if you decide against an LP or are unsuccessful or get a bloody tap): give treatment as per Table B1 (New) or Table B2 (Previous), and treat for meningitis with IM chloramphenicol.
- Clear CSF (see Coma, p.82): treat for cerebral malaria (the CSF may contain a few cells with a slightly raised protein). Give treatment as per Table B1 (New) or B2 (Previous). Do daily parasite density counts. Restrict the fluid intake to two-thirds maintenance (Coma regime as per STB). Monitor BP, hydration, blood sugar (eg dextrostix), urine output, Hb, urea and electrolytes. Hypoglycaemia is common in severe malaria (New Engl J Med 319:1040-7,1988).

Treatment B1 (New)

IM Artemether (80 mg/ml):
Give IM once daily until child improves (3.2 mg/kg day 1, 1.6 mg/kg thereafter).
Note: The dose on the first day is different from the dose on the following days.
When the child has improved and can take oral treatment, give

Oral Artesunate (tab 50 mg):
Give once daily to complete a total of 7 days (2.5 mg/kg).
Give a single dose of Fansidar on day 3 of treatment or on the first day of oral treatment if this is after day 3.

Severe malaria: Treatment Chart B1 (New)

Weight (kg)	IMI Artemether Day 1	IMI Artemether Day 2-7	Oral Artesunate Day 2-7	Oral Fansidar Single dose Day 3
3 - 5.9	0.25 ml	0.25 ml	¼ tab	¼ tab
6 - 12.9	0.5 ml	0.25 ml	½ tab	½ tab
13 - 18.9	0.75 ml	0.5 ml	¾ tab	1 tab
19 - 24.9	1 ml	0.5 ml	1 tab	1½ tab
25 - 30.9	1.25 ml	0.75 ml	1½ tab	2 tab
31 - 36.9	1.5 ml	0.75 ml	1½ tab	2 tab
37 - 43.9	1.75 ml	1 ml	2 tab	2½ tab
>44	2 ml	1 ml	2 tab	2½ tab

The dose of Artemether on day 1 is bigger than the dose for the following days.
Change to oral treatment as soon as the patient can take it.
Continue treatment for 7 days.
Give a single dose of Fansidar on day 3 of treatment or on the first day of oral treatment if this is after day 3.

Treatment B2 (Previous but without the single dose of primaquine)

Severe malaria: Treatment Chart B2 (Previous)

Weight (kg)	IMI Quinine Twice daily	Oral Quinine 3 times daily	Fansidar Single dose
3 - 3.9	0.5 ml	¼ tab	¼ tab
4 - 5.9	1 ml	¼ tab	¼ tab
6 - 9.9	1.5 ml	¼ tab	½ tab
10 - 14.9	2 ml	½ tab	1 tab
15 - 19.9	3 ml	½ tab	1 tab
20 - 24.9	4 ml	1 tab	1½ tab
25 - 29.9	5 ml	1 tab	1½ tab
30 - 39.9	6 ml	1½ tab	2 tab
Quinine:	IMI Quinine (120 mg/2 ml): Twice daily until child improves, then Oral Quinine (300 mg tab): 3 times daily for 3 days.		
Fansidar:	Single dose on first day of oral treatment.		

TREATMENT FAILURE MALARIA

This is defined as the persistence of P falciparum trophozoites for 7 days, or recurrence within 4 weeks, after an **adequate, supervised** and appropriate course of treatment for uncomplicated malaria (either New, A1, or Previous, A2). Do daily trophozoite counts if you suspect treatment failure (likely to be the result of drug resistance):

- you must be certain the child did not vomit or spit out the drugs.

(Note: Resistance to amodiaquine or chloroquine is mainly a problem with P falciparum, but cases of resistant vivax are becoming more common and P falciparum resistant to Fansidar is also well established).

Treat with oral Artesunate and single dose Fansidar (Chart C1, New regimen) or with quinine and Fansidar (C2, Previous regimen).

Treatment C1 (New)

Oral Artesunate (tab 50 mg):
Give once daily for 7 days (5 mg/kg day 1, 2.5 mg/kg thereafter).
Note: The dose of Artesunate on day 1 is bigger than the dose on the following days.

Oral Fansidar:
Give a single dose on day 3 of treatment.

Treatment failure malaria: Treatment Chart C1 (New)

Weight (kg)	Oral Artesunate Day 1 Single dose	Oral Artesunate Day 2-7 Once daily	Oral Fansidar Day 3 Single dose
4 - 5.9	½ tab	¼ tab	¼ tab
6 - 8.9	¾ tab	½ tab	½ tab
9 - 12.5	1 tab	½ tab	1 tab
12.6 - 18.5	1½ tab	¾ tab	1 tab
18.6 - 24.9	2 tab	1 tab	1½ tab
25 - 31.9	2½ tab	1½ tab	2 tab
32 - 37.5	3 tab	1½ tab	2 tab
37.6 - 50	4 tab	2 tab	2½ tab
If you do not have any Artesunate, use Quinine and Fansidar:			
Quinine (tab 300 mg):	Give oral 3 times daily for 3 days (see Treatment C2)		
Fansidar:	Give a single dose on the first day of treatment.		

Treatment C2 (Previous but without the single dose of primaquine)

Treatment failure malaria: Treatment Chart C2 (Previous)

Weight (kg)	Oral Quinine 3 times daily	Fansidar Single dose
3 - 3.9	¼ tab	¼ tab
4 - 5.9	¼ tab	¼ tab
6 - 9.9	¼ tab	½ tab
10 - 14.9	½ tab	1 tab
15 - 19.9	½ tab	1 tab
20 - 24.9	1 tab	1½ tab
25 - 29.9	1 tab	1½ tab
30 - 39.9	1½ tab	2 tab
Oral quinine (300 mg tab):	Give 3 times daily for 3 days	
Fansidar:	Give single dose on day 1 of treatment	

COMPLICATIONS OF ACUTE MALARIA

Hyperpyrexia (temperature over 40 °C)

Hyperpyrexia may cause convulsions. It may be associated with cerebral malaria. Give antimalarials, paracetamol, cool sponge and fan.

Anaemia

In acute malaria, the anaemia is usually normochromic and normocytic. However, it is frequently hypochromic and microcytic due to an associated iron deficiency anaemia; the red blood cells show polychromasia and there is a raised reticulocyte count indicating the haemolytic element of the anaemia. A haemoglobin of 6 g/dl or less is an indication for urgent blood transfusion. Give 20 ml/kg of packed cells. To prevent precipitating heart failure, give IV frusemide (Lasix) once the blood transfusion has started. Do NOT give frusemide if the child has diarrhoea or is dehydrated.

Hypoglycaemia

Hypoglycaemia is common in children with severe malaria, and is associated with a high mortality (Lancet 1:708-711,1987). Do a dextrostix and give 5 ml/kg 10% dextrose (or 1 ml/kg 50% dextrose) IV over 15 min if the blood glucose is less than 40 mg% (2.2 mmol/l).

Dehydration

This is often caused by severe vomiting and diarrhoea. Correct the dehydration with half strength Darrow's solution IV.

Algid malaria

This is severe malaria associated with shock. It is often caused by gram negative sepsis (as well as malaria). The child is usually dehydrated from severe diarrhoea or vomiting or both. The child may also have cerebral malaria. Commence treatment for severe malaria immediately (Treatment B1 or B2). Take blood and urine cultures, then give IV chloramphenicol, or ampicillin and gentamicin. Give 20 ml/kg of normal saline fast, then half strength Darrow's solution.

Blackwater fever

Severe intravascular haemolysis causes methaemalbumin in plasma and haemoglobinuria, which makes the urine dark. Haemoglobinuria has a number of causes (see p.382), but is called blackwater fever when caused by *P falciparum* infection. Blackwater fever is probably due to the production of auto-antibodies in response to immunological changes in parasitized red blood cells. It may occur more often when quinine is used. It may also occur with G6PD deficiency. Give treatment for severe malaria (Treatment B1 or B2), keep a careful record of the child's fluid balance (do NOT overhydrate) and, if anuria develops, consider starting peritoneal dialysis. Give a blood transfusion if the Hb is 6 g/dl or less. Exchange transfusion may be needed in severe cases.

Liver failure

A slight degree of jaundice due to haemolysis is quite common in severe acute malaria. Occasionally, however, there is progressive jaundice and liver failure due to liver cell damage.

MALARIA PROPHYLAXIS

Prevention of mosquito bites

The incidence of malaria can be reduced by lowering the risk of mosquito bites: wearing clothes that cover the arms and legs at night, using insect repellants (including pyrethrin burning coils at night), covering windows and doorways with wire-netting and using residual insecticide sprays in dwellings. Mosquito nets have been shown to be effective in Papua New Guinea and are more effective if they are impregnated with the insecticide permethrin.

Drugs for prophylaxis

No drug destroys the sporozoites, therefore true prophylaxis is impossible. Proguanil and pyrimethamine kill the pre-erythrocytic forms of P falciparum and they therefore prevent initiation of the erythrocytic cycle. This is sometimes called "causal prophylaxis". For a review of antimalarials, see Antimicrob Agents Chemother 32:953-61,1988.

The indications for prophylaxis in children are:
- as part of the treatment of anaemia (3 months)
- tropical splenomegaly syndrome
- severe malnutrition.

From a practical point of view, it is easiest to treat children in these groups with chloroquine or infant Camoquin 5 mg/kg weekly. Breakthrough malaria would then be treated as chloroquine resistant/treatment failure malaria. In particular cases, it might be necessary to advise other prophylaxis in addition to or instead of chloroquine.

Paediatricians and medical officers are sometimes asked to give advice to parents of non-immune children travelling to areas of high malaria transmission. As a general rule, parents of expatriate children should be encouraged to follow the advice provided by the health authorities of their own countries. Alternatively, the WHO recommendations currently in force can be followed (at present this is weekly mefloquine).

There are worries about the use of mefloquine - though the risks may have been overstated. Fansidar has been used but may not be effective. For children aged 10 years or older, tetracycline or doxycycline may well be effective. Proguanil is another alternative, though probably less effective. For children older than 5 years, Maloprim (pyremethamine and dapsone) has been used, but there are worries about its safety. It is definitely contraindicated in children less than 5 years of age (Maloprim may cause methaemoglobinemia).

Chloroquine or infant Camoquin should be taken in addition to Maloprim to provide some protection against vivax malaria.

NOTES ON DRUGS USED TO TREAT OR PREVENT MALARIA

Artemisinin and its derivatives

Artemisinin (qinghaosu) and its derivatives. Qinghaosu - a herbal product from Qinghao or sweet wormwood - has been used in China for thousands of years. A number of compounds derived from Qinghao has been isolated and are now available for use. They include:
- artemisinin, the parent compound
- dihydroartemisinin
- artesunate, metabolised to dihydroartemisinin
- artemether, metabolised to dihydroartemisinin.

Dihydroartemisinin is available in oral and suppository form.
Artesunate is available in oral and parenteral form - but the latter is complicated to use.
Artemether is available in oral and parenteral form. It is soluble in oil and, as an intramuscular injection, has been used successfully, easily and safely, including in a WHO collaborative study in PNG. It is also available in suppositories.

The Health Department has decided to opt for artemether IMI and artesunate tablets. Other preparations are available through the private sector. Doctors must be familiar with the correct doses. Artemisin or artemether suppositories may become available in the future for the treatment of children with severe malaria.

Chloroquine and amodiaquine

1. A treatment course of either drug is 25 mg/kg over 3 days.
2. The usual oral dose is 10 mg/kg daily for 3 days.
3. Prophylactic chloroquine in the correct dose does NOT cause retinopathy - even after many years.

4. Prophylactic amodiaquine has been associated with agranulocytosis in adults (Lancet 1:411-414,1986). The risk may be as high as 1/2000, so it is no longer recommended for prophylaxis in adults.

Quinine

With the introduction of artemether, quinine is likely to become a reserve drug for use in severe malaria if artemether is not available or if artemether resistance develops. It will, however, still be used for severe malaria in the first trimester of pregnancy.

If used in children, quinine is given 12 hourly IM until the patient improves. Oral quinine is then given for 3 days and a dose of Fansidar given on the first day of oral treatment.

Occasionally, quinine is given intravenously. The dose (10-15 mg/kg/dose) is given in 10 ml/kg of 5% or 10% dextrose over 4 hours.

Fansidar

Because of the high levels of chloroquine and amodiaquine resistance in Papua New Guinea, Fansidar is now part of the treatment for uncomplicated malaria, together with amodiaquine or chloroquine. Fansidar (pyrimethamine and sulphadoxine) kills the malarial parasites in a similar way to that in which cotrimoxazole (Septrin) kills bacteria, by blocking steps in the synthesis of purines.

Fansidar takes some time to act and should not be used alone. It has a half-life of 4 to 8 days. Fansidar has been associated with agranulocytosis and also causes Stevens-Johnson syndrome (exfoliative dermatitis); the incidence may be as high as 1/5000 (MMWR 34:185-195,1985). Other side effects of Fansidar include less severe skin rashes, nausea, vomiting, thrombocytopenia, megaloblastic or haemolytic anaemia, methaemoglobinaemia and jaundice.

Maloprim

Maloprim contains dapsone (a sulphone) and pyrimethamine. It is slow-acting, and has been used successfully for the prevention of falciparum malaria in chloroquine-resistant areas. It is not preventative for vivax, so chloroquine is needed as well. Maloprim is no longer recommended because of the risk of agranulcytosis. The incidence of this complication when Maloprim is given twice a week may be as high as 1/2500 (Br Med J 282:988,l981) though it appears to be considerably less when given once weekly. It has been associated in Papua New Guinea with a fixed drug eruption.

Primaquine

Primaquine has been used as a gametocidal as a strategy to prevent transmission. Its benefit for this purpose has not been proven and it has been removed from the new standard treatment regimens.

To treat the exoerythrocytic (liver) phase of P vivax, malariae or ovale, give 0.25 mg/kg oral for 14 days. Nausea and abdominal discomfort are very common. Haemolysis may occur in G6PD deficient patients. Cyanosis may occur due to methaemoglobinaemia.

Mefloquine

Mefloquine is a derivative of quinine, and has a long half-life. It is active against many strains of P falciparum that are resistant to other drugs, but some resistant strains have already been reported. Mefloquine is expensive and a high incidence of side effects, particularly vomiting in children and neuropsychiatric problems in adults, have been reported, though these have probably been over-emphasised. It is the WHO's currently recommended prophylactic for travellers to Papua New Guinea.

Other drugs

Tetracycline or doxycycline are effective prophylactic agents. They are given daily, as is proguanil.

PARASITE DENSITY

This is expressed as the number of parasites seen per number of high powered fields (HPF) examined, eg 150/10 means 150 parasites were seen in a total of 10 HPF (ie 15 parasites per HPF).

- Under 10 parasites per HPF - mild infection
- 10 - 50 parasites per HPF - moderate infection
- Over 50 parasites per HPF - severe infection

Serial parasite densities are useful in monitoring the progress of an individual patient. If 5% of a patient's red blood cells are parasitised, the prognosis is poor, and recovery is unusual if 10% or more of red cells are parasitised

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