

Chapter 8

Clinical Features Of Malaria In Pregnancy And Children

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The first section of this paper will deal with the clinical features of malaria in pregnancy, while the second will cover the same topic in children.

I Malaria in pregnancy

In areas of unstable malaria (and in non-immune pregnant mothers originating from non-endemic countries), pregnant women are susceptible to all the manifestations of severe malaria described in Chapter 7. Moreover, they have an increased risk of abortion, stillbirth, premature delivery and low birth weight of their infants (Wickramasuriya 1937; Menon 1972). Malaria mortality rate in this group of pregnant women is 2-10 times higher than in non-pregnant women (Brabin 1983 & 1991).

Falciparum malaria commonly induces uterine contractions and gives rise to premature labour. The frequency and intensity of contractions appear to be related to the height of the fever (Looaresuwan et al, 1983). Foetal distress is common but often not diagnosed. The prognosis for the foetus is poor.

Only two of the common clinical features will be re-emphasised here, namely - hypoglycaemia and pulmonary oedema.

Hypoglycaemia

Pregnant women are particularly prone to hypoglycaemia which may occur in otherwise uncomplicated disease. It is also commonly encountered on admission in severe disease or may result during the course of quinine therapy (White et al 1983) .

Hypoglycaemia may be asymptomatic or may present with sweating, abnormal behaviour, convulsions or a deteriorating level, or sudden loss of consciousness.

Acute Pulmonary Oedema

This complication is associated with a very high mortality. It may occur on admission; it may develop suddenly and unexpectedly at a time when other symptoms are subsiding and the parasitaemia has significantly dropped or even disappeared - or it may occur immediately after delivery (Fig. 1).

In areas of stable malaria the classical manifestations of severe disease are rare in partially immune pregnant women. In these, and particularly in primigravidae, abortion, stillbirth, premature delivery and low birth weight of their new-born infants are the commonest findings (Wickramasuriya, 1935; Archibald 1956; Menon, 1972; Bray and Anderson 1979; McGregor et al 1983; Morgan 1994; Greenwood et al 1994). Parasite rates and densities are greater in pregnant than non-pregnant women, especially in primiparae. The other clinical consequence that is found is anaemia (Fig. 2), which bears little relation to the peripheral parasitaemia (Gilles et al 1969; Rougemont et al 1977; Brabin 1983; McGregor 1984; Steketee et al 1994; Matteelli et al 1994). Once again, primiparae are much more likely to be affected.

Management

The management of hypoglycaemia, pulmonary oedema, anaemia and the other severe manifestations of malaria is similar to that described in Chapter 11.

Monitoring of uterine contractions and foetal heart rate is imperative, while foetal or maternal distress may require early obstetric intervention, if labour has started.

Prevention

For non-immune pregnant mothers, chemoprophylaxis is advisable because malaria infection carries a greater risk of severe disease. In areas where resistance to chloroquine does not exist, or is predominantly RI, chloroquine with proquanil together with stringent personal protection measures (repellents, protective clothing, house screens, impregnated bed nets) often gives a good measure of protection. Breakthroughs can and do occur and must be diagnosed and treated promptly.

Mefloquine given from the second trimester onwards has proved safe and effective in areas where proquanil and chloroquine cannot be used (Steketee et al 1994; Nosten, 1994). The increasing reports of side effects from this drug may limit its usefulness in the future.

For semi-immunes and particularly primigravidae, chemoprophylaxis has been shown to be effective in several trials in Africa, in reducing the two most important clinical consequences of malaria in this group - low birth weight of infants and anaemia. (Fleming et al, 1986; Greenwood et al, 1989; Greenwood et al, 1994). Unfortunately, chloroquine which was the drug most frequently used is no longer effective in many areas. Mefloquine has been shown to be a good substitute, but it is expensive and increasing reports of side effects are a cause for anxiety.

In order to overcome some of the problems encountered in the prevention of malaria in pregnancy, namely - increasing frequency and intensity of resistance to *P. falciparum*, contraindications of some of the antimalarials, poor compliance due to a variety of reasons - simplified regimes are undergoing clinical trials using sulphonamide-pyrimethamine combinations (where these are still effective, e.g. Africa) given at the first attendance (providing it is in the second trimester) and repeated once again at the beginning of the third trimester (WHO, 1994).

Congenital Malaria

In endemic areas, vertical transmission of malaria across the placenta is common (Steketee et al 1994), but parasitaemia often disappears within a few days after birth (Nyirjesy et al 1993).

Symptomatic malaria - fever, anaemia, hepatosplenomegaly - are however rare (Covell 1950; Logie and McGregor 1970). Passive immunity derived from the semi-immune mothers together with other factors e.g. high concentration of foetal haemoglobin, may be responsible (Edozien et al 1962; Pasvol et al, 1980).

II Malaria in Children

It is important to realise from the outset that malaria in indigenous children inhabiting highly endemic areas and thus continuously exposed to infection are, until the age of about 5 years highly susceptible to all the manifestations of *P. falciparum* malaria. Indeed, it is estimated that about 1,000,000 children aged between 1 and 5 years die every year from the disease. Because primary health services are poorly developed in many malaria endemic countries, it is very likely that most of these children die without reaching a health facility (Greenwood et al, (1987). The children that survive this critical period, achieve, after several successive attacks, a relative tolerance of the infection - semi-immune - and in these, malaria is either asymptomatic despite a parasitaemia of 10% to 30%, or mild, with non-specific symptoms, such as mild fever, fretfulness, anorexia, sweating and anaemia. Hepatosplenomegaly is also common.

The incubation period of *P. falciparum* is 7-15 days; of *P. vivax* usually 10-20 days; of *P. ovale* 11-16 days and of *P. malariae* 30-40 days or longer.

Clinical features

a. *P. Falciparum malaria*

The non-immune child with uncomplicated malaria often appears listless, restless or drowsy, refuses food and if old enough, may complain of headache or nausea. Pallor of the skin, nails and mucous membranes may occur. Thirst may be marked as the temperature rises; breast-fed infants make frequent attempts to suck the breast, but this is soon abandoned, possibly due to nausea. A clear cut cold stage with rigor, hot stage and sweating stage are uncommon. Vomiting is often marked and the vomitus bile-stained, while the stools may be loose and dark green, but no blood or pus cells are seen. Infants may seem in abdominal distress while older children complain of pain over the liver or spleen. Constipation is not uncommon. The temperature is often high (40°C), continuous and irregular and the child is flushed and sweaty. Even when the temperature is only moderately high, febrile convulsions can often occur. Unless consciousness returns within about 30 minutes, cerebral malaria must be suspected. The liver is often enlarged and tender, followed by enlargement of the spleen. Ophthalmological examination of the fundi should be carried out because the presence of retinal haemorrhages is an indication of impending severe disease (Fig. 3).

The diagnosis of uncomplicated malaria in semi-immune children is more complex because so many of them can have an asymptomatic parasitaemia ranging from 2%-30%, hepatosplenomegaly and their symptoms may be due to a variety of other illnesses; the parasitaemia being incidental rather than causal. As reasonable a set of criteria as any for the diagnosis of uncomplicated malaria in these children is (1) fever, for which no other cause can be found on physical examination, (2) a parasitaemia of 10,000 parasites per ul if microscopic examination is available, (3) response of fever and other symptoms within 48-72 hours, (4) diminution of parasitaemia unless RII resistance is suspected (Gilles & Warrell, 1993).

Since microscopical facilities are rarely available in primary health centres, other definitions have been sought. The most recent clinical algorithm has identified three signs - temperature 37.7°C or higher; splenomegaly or pallor of the nailbeds. In Malawi, this combination was 85% sensitive in identifying parasitaemic children and 41% specific (Redd et al, 1996).

A delay in diagnosis and treatment in non-immune children as short as two to three days usually results in the development of the various syndromes associated with severe *falciparum malaria* (see Chapter 7). Some of these, namely - renal failure; pulmonary oedema and spontaneous bleeding (DIC), are rare in children and have already been described in Chapter 7. The commonest and most important manifestations of severe malaria in children are: (1) cerebral malaria (2) anaemia (3) metabolic acidosis (4) hypoglycaemia (5) hyperpyrexia (6) hyperparasitaemia (7) circulatory collapse (8) haemoglobinuria. In this context, it is important to remember that multiorgan failure i.e. the presence of more than one of the above manifestations occurring in the same patient is a common occurrence in severe malaria.

1. Cerebral malaria

Cerebral malaria usually but not always presents with fever (37.5°-41°C), and a history of failure to eat or drink, vomiting, cough, impaired consciousness and moderate dehydration. Diarrhoea is unusual. Hepatosplenomegaly is usual. Convulsions are common and may occur at any age and any temperature. The depth of coma is variable and should be assessed using the Blantyre scale and regularly monitored throughout the course of the illness. In some children, the breathing is laboured and noisy; deep breathing with a clear chest clinically and/or radiologically suggests acidosis (see later). Retinal abnormalities including haemorrhages, vessel obstructions, macular or extramacular oedema and papilloedema occur (Llewallen et al, 1993). Jaundice and spontaneous bleeding are rare (Molyneux et al, 1989).

Neurological abnormalities are very variable and include opisthotonos (Fig. 4), decerebrate or decorticate rigidity, hypotonia, abnormal plantar reflexes, absent abdominal, corneal and vestibulo-ocular reflexes, conjugate deviation of the eyes and grinding of the teeth (Bruxism) (Molyneux et al, 1989, WHO, 1996). CSF opening pressure is raised (Newton et al, 1991).

Plasma urea and creatinine concentrations are often elevated on admission, but revert to normal following rehydration. Hypoglycaemia and acidaemia (particularly hyperlactataemia) are often associated with cerebral malaria (White, 1986; Taylor et al, 1993; Marsh et al, 1995; WHO 1996).

Most surviving children with cerebral malaria make a full neurological recovery, but about 11% develop neurological sequelae. The most reported sequelae include - ataxia, hemiplegia, speech disorders, blindness, behavioural disturbances, hypotonia, general spasticity, tremors, visual and auditory hallucinations (Brewster et al, 1990; WHO, 1996).

Fortunately, most children with sequelae show considerable improvement and sometimes even complete recovery after the passage of time (Schmutzhard et al 1984; WHO, 1996).

2. Anaemia

Anaemia is an important manifestation of severe malaria. It is most commonly seen in children under 2 years of age. It may occur alone or in combination with other manifestations of severe malaria e.g. cerebral malaria; metabolic acidosis. Breathing difficulties in an anaemic child are more likely to be due to metabolic acidosis than cardiac failure (WHO, 1996).

The rate of development and the degree of anaemia depend on the severity and frequency of parasitaemia. In some children, repeated untreated or inadequately treated attacks of otherwise uncomplicated malaria will result in a progressive normochromic anaemia in which dyserythropoic changes in the bone marrow are prominent. Parasitaemia is often scanty, and a presumptive diagnosis of a malarial aetiology is based on finding numerous pigmented monocytes in the peripheral blood.

In other children, severe anaemia may develop rapidly in association with hyperparasitaemia. In these cases, acute haemolysis of parasitized red cells is mainly responsible. Severe anaemia is however multifactorial and the haematological picture may be variable.

3. Metabolic acidosis

Acidaemia (defined as an arterial pH less than 7.25) or acidosis (plasma bicarbonate concentration less than 15mmol/l), is an important manifestation of severe malaria. It can occur independently, or in association with other manifestations of severe malaria, particularly cerebral malaria, anaemia, hypoglycaemia and hypovolaemia (Taylor et al, 1993; Krishna et al, 1994; Marsh et al, 1995). The major contribution to acidosis is hyperlactataemia (5mmol/l; normal range up to 2mmol/l). Lactic acidosis should be suspected if the anion gap ($\text{No}^+ - (\text{Cl}^- + \text{Hco}_3^-)$ mEq/l) exceeds 10 to 12 mEq/l (OH & Carrol, 1977).

Respiratory distress manifested by deep breathing (increased inspiratory and expiratory excursion of the chest) is a reliable clinical indicator of metabolic acidosis. It is important to note in this context that the overlap between severe malaria presenting with respiratory distress and acute respiratory infections (ARI) is considerable. It is extremely difficult on clinical grounds to distinguish between severe malaria presenting with cough, breathing difficulties and a raised respiratory rate, and pneumonia (O'Dempsey et al, 1993).

In situations where neither x-ray facilities nor microscopic examination are available, or when in doubt, it is prudent to treat children presenting with fever and respiratory symptoms, for both malaria and ARI (WHO, 1996).

4. Hypoglycaemia

Hypoglycaemia commonly occurs in children under 3 years. It is a frequent presenting symptom in malaria, as well as other childhood illnesses (Solomon et al, 1994). It is associated with convulsions, profound coma, hyperparasitaemia, lactic acidosis and high levels of circulating tumour necrosis factor (WHO, 1996).

In contrast to adults, it rarely occurs as a result of quinine therapy. It is easily overlooked clinically because its features may be similar to those of cerebral malaria. It is imperative therefore to measure on admission whole blood glucose of all children suffering from severe malaria. (Stix method and/or biochemically).

5. Hyperpyrexia

High fever is common in children suffering from severe malaria. Although convulsions may occur at any level of body temperature, they more commonly occur at temperatures above 38.5°C. (Familusi & Sinnette, 1971). Hyperpyrexia can result in coma.

6. Hyperparasitaemia

The interpretation of hyperparasitaemia varies in different areas, in unstable areas, a peripheral parasitaemia in non-immune children of 4% is indicative of severe malaria (WHO, 1996). In areas of stable malaria, threshold levels of 20% or greater should be considered to indicate severe malaria (WHO, 1996), although local experience, if available, may prove otherwise.

7. Circulatory collapse (see also Chapter 7)

The diagnosis of shock in children is based on a combination of hypotension (BP 50 min/Hg. or less), weak or absent peripheral pulses and coolness of the mid to proximal limbs.

8. Haemoglobinuria (see also Chapter 7)

Dark red or black urine occurs in children usually associated with hyperparasitaemia in the absence of G6.P.D. deficiency.

Diagnosis

The differential diagnosis of severe malaria in children will have to take into consideration the common childhood diseases, especially if the child has not been immunised against them e.g. diphtheria and tetanus. A bulging fontanelle or neck stiffness would suggest meningitis; although its absence does not exclude it. Sepsis in any limb or organ, should be looked for. Tonsillitis and chronic otitis media should be excluded.

As has already been pointed out, two of the most important differential diagnoses are acute respiratory infection (ARI) and pneumonia. Enlarged lymph nodes could be a pointer to other alternative diagnoses - e.g. trypanosomiasis, tuberculosis and other numerous possibilities.

A rash would suggest typhus, typhoid, an arbovirus infection, relapsing fever, chickenpox, measles, or meningococcaemia.

The differences between severe malaria in adults and children are given in Table 1.

Table 1

Differences between severe malaria in adults and in children^a

Sign or Symptom	Adults	Children
Cough	Uncommon early symptom	Common early symptom
Convulsions	Common	Very common
Duration of illness	5 - 7 days	1 - 2 days
Resolution of coma	2 - 4 days	1 - 2 days
Neurological sequelae	Uncommon	10% (approx)
Jaundice	Common	Uncommon
Pretreatment hypoglycaemia	Uncommon	Common
Pulmonary oedema	Common	Rare
Renal failure	Common	Rare
CSF opening pressure	Usually normal	Often raised
Bleeding/clotting disturbances	Up to 10%	Rare
Abnormality of brain stem reflexes (e.g. oculovestibular, oculocervical)	Rare	More common

^a Derived from studies in South-East Asian adults and African children (Warrell et al 1989; Molyneux et al, 1989; WHO 1996)

Management

The management of severe malaria in children is basically similar to that described for adults (Chapter 11); a summary of which is given in Table 2. A few particular measures will be re-emphasised here. The most important maxim is frequent monitoring and reassessment; initially at hourly or 2-hourly intervals, if possible.

Convulsions

It is important to note whether the child has received diazepam or paraldehyde before admission to hospital and when, since this is a frequent occurrence, and another injection is inadvisable.

Diazepam should be given intravenously by slow injection at an initial dose of 0.3mg/kg (rate not to exceed 2mg/min) or interrectally at a dose of 0.5mg/kg.

Paraldehyde is safe and effective and can be given to children who have already received diazepam. The dose is 0.2ml/kg by deep intramuscular injection, or 0.4ml/kg intrarectally.

Hypoglycaemia

This is treated with 25% or 50% dextrose (0.5gm/kg) given intravenously over several minutes. Glucose solution can be given by nasogastric tube if intravenous infusion is not possible.

Metabolic acidosis

Correct any reversible cause of acidosis; particularly dehydration and severe anaemia. If the haemoglobin is < 5g/dl and the child has respiratory distress, blood transfusion 20ml/kg given over 4-6 hours is given. If the haemoglobin is >5g/dl with respiratory distress, give normal saline in aliquots of 10ml/kg, the speed of infusion being based on clinical judgement (WHO, 1996). If any doubt exists as to whether ARI may be the cause of respiratory distress, give parenteral antibiotic therapy in addition to the above management.

Severe anaemia

The decision of when to transfuse must be based on careful clinical judgement and particular needs of individuals, rather than on a laboratory-based formula.

Chemotherapy (see also Chapters 10 & 11)

The Chemotherapy of severe malaria in children is given in Chapter 11. Areas of the world where chloroquine resistance has not been reported are so few and the resistance situation so dynamic that quinine is the drug of choice.

In circumstances where one can be certain that *P. falciparum* parasites are fully sensitive to chloroquine, then this drug is preferable to quinine - it acts faster and does not produce hypoglycaemia. It must however be given in the correct dosage, correct route, correct rate of infusion and frequency.

If for some reason quinine or quinidine is not available, then it is justified to use parenteral chloroquine, even if resistance is known to occur, in the hope that the majority of cases would only be RI or RII resistant.

In areas where multidrug resistance occurs, artemisinin and its analogues are the drugs of choice given by intramuscular or intravenous injection, or as suppositories (see Chapters 10 and 11).

Prognosis

The major indicators of a poor prognosis in children with severe malaria are listed below (Grau et al, 1989; WHO, 1996)

A Clinical Indicators

- Depth of coma
- Witnessed convulsions
- Age < 3 years
- Papilloedema and/or retinal oedema
- Respiratory distress (deep inspiratory and expiratory breathing)
- Absent corneal reflexes

B. Laboratory Indicators

- Parasite density > 1 million/ul
- Peripheral schizontaemia
- Peripheral leucocytosis (>12,000/ul)
- Large size of ring-stage parasites in peripheral blood
- Intraleucocytic malaria pigment
- Hypoglycaemia (<2.2 mmol/l - <40mg/dl)
- Metabolic acidosis (pH < 7.3 : base-excess < -12)
- Increased plasma lactate concentrations (> 6mmol/l)
- Increased CSF lactate concentrations (> 6mmol/l)
- Severe anaemia (Hb < 5.0g/dl or PCV < 20%)
- Increased plasma concentrations of tumour necrosis factor (TNF)

It must be appreciated however, that regional differences in presentation, prognostic factors and mortality, occur. Thus, whereas cerebral malaria seems to be the commonest presentation in West Africa; anaemia is the commonest presentation in Papua New Guinea (Waller et al, 1995; Modiano et al, 1995; Allen et al, 1996). Large size ring-stage parasites in the peripheral blood are sometimes seen in asymptomatic children in stable areas of West Africa.

6. Vivax and Ovale malaria

Ovale malaria is clinically milder than vivax, otherwise, the clinical features are similar. Some strains of *P. Vivax*, especially those from temperate regions, have a long incubation period, up to 8 - 14 months.

Prodromal symptoms are non-specific and include restlessness, drowsiness, anorexia, headache and nausea. Fever is at first irregular, remittent, or quotidian, later becoming tertian if the child is not treated early. It occurs by day and usually develops in the afternoon. Febrile convulsions are not uncommon but cerebral malaria does not occur. The classical febrile paroxysm consisting of the cold stage (15m - 60m); the hot stage (2 hours or more) and the sweating stage are uncommon in infants and children. Hepatosplenomegaly is common and a moderate anaemia may be found. Parasitaemia may be less than 2% of erythrocytes infected; all stages of the asexual cycle are usually found in the peripheral blood, with gametocytes appearing after a week of the clinical course.

If a blood schizonticide only is given, relapses occur after a period of quiescence, weeks or months after the initial attack.

The treatment of vivax and ovale malaria is given in Chapters 10 and 11.

Resistance of *P. Vivax* to chloroquine has been reported (Papua New Guinea, Irian Jaya) but is at present extremely rare. For practical purposes, chloroquine remains the drug of choice for the treatment of *vivax* and *ovale* malaria. Radical cure can only occur if primaquine is given in addition to chloroquine. Some strains e.g. Chesson strain of *P. vivax* require the longer course of primaquine recommended (21 days). It is only advocated if the child no longer continues to live in an endemic area. If he/she continues to live in an endemic area and is therefore at continual risk of reinfection, treatment of the overt attack only with chloroquine is advocated.

If the child has G6PD deficiency a weekly dose of primaquine of 7.5mg/kg for 8 weeks, also produces a radical cure and diminishes the risk of a drug-induced haemolysis.

C. Quartan malaria (*Malariae malaria*)

The clinical picture is basically similar to that of *vivax* malaria, except that the periodicity of the fever, when established, is quartan (every 72 hours) instead of tertian (every 48 hours).

The most important clinical manifestation is the development of the nephrotic syndrome, often referred to as quartan malarial nephropathy (QMN). Despite numerous reports on the association between *P. malariae* and the nephrotic syndrome (Fig. 5), a notable tone of incredulity still existed among physicians, both in non-endemic and endemic malaria areas. Thus, Luder (1958) concluded that the association was still unproven, while Trowell (1960) suggested that the time was ripe for the reassessment of the whole problem. The association was first confirmed statistically in Nigeria (Fig. 6) by Gilles and Hendrickse (1963) and later in East Africa (Kibukamusoke et al, 1967; Kibukamusoke, 1973). Meanwhile, the decline in the prevalence of the nephrotic syndrome which followed malaria eradication in Guyana lent further support for the causal relationship (Giglioli, 1962). It was postulated that the most likely mechanism was an immune complex nephropathy (Gilles and Hendrickse, 1963). Subsequent immunological studies confirmed the hypothesis that glomerular damage was due to immune complex deposition (Ward and Kibukamusoke, 1969; Hendrickse et al, 1972) and the presence of *P. malariae* antigen in the glomeruli was demonstrated. Renal biopsy studies suggested that there may be a morphologically specific lesion (White, 1973).

Children between 4-8 years are most commonly affected and they usually present with severe generalised oedema; persistent heavy proteinuria; severe proteininaemia and ascites (Fig.7); azataemia or hypertension are very uncommon.

Symptomatic and supportive treatment consists of diuretics and high protein diet. Antimalarial, steroid and immunosuppressive therapy of QMN have given disappointing results (Gilles and Hendrickse, 1963; Adeniyi et al, 1970; Wing et al, 1972).

The treatment of uncomplicated quartan malaria is given in Chapters 10 and 11.

Diagnosis

The diagnosis of malaria in children can be conveniently divided into (I) clinical, (ii) parasitological (iii) immunological and (iv) molecular (see Chapter 9).

From the clinical standpoint, the most important factor is to have a high index of suspicion that malaria is a likely diagnosis and hence to always take a travel history when interrogating the child or the parents. It must always be appreciated that malaria can clinically mimic many other diseases. The commonest misdiagnoses in children are ARI, pneumonia and meningitis.

Table 2

Summary of the management of severe and complicated Falciparum malaria (Gilles 1991)

Manifestation/complication	Immediate management ^a
1. Coma (cerebral malaria)	Maintain airway; nurse on side; exclude other treatable causes of coma (eg hypoglycaemia, bacterial meningoencephalitis). Give prophylactic anticonvulsant (10mg of phenobarbitol sodium per kg of body weight intramuscularly). Avoid harmful adjuvant treatments such as corticosteroids, heparin and epinephrine (adrenaline).
2. Convulsions	(Prevent with intramuscular phenobarbitol sodium, see above). Maintain airway; treat with diazepam given intravenously or per rectum (0.15 mg/kg to a maximum of 10 mg) or intramuscular paraldehyde injection (0.1 ml/kg from a glass syringe)
3. Severe anaemia	Transfuse fresh whole blood or packed cells
4. Acute renal failure	Exclude dehydration; maintain strict fluid balance; carry out peritoneal dialysis (or haemodialysis if available)
5. Hypoglycaemia	Measure blood glucose, give 50% glucose injection 50 ml (1ml/kg for children) followed by 5% or 10% glucose infusion
6. Metabolic acidosis	Exclude or treat hypoglycaemia, hypovolaemia and Gram-negative septicaemia. Give oxygen. Correct arterial pH to 7.2 or above. Blood transfusion. Crystalloid infusion
7. Acute pulmonary oedema	Prevent by avoiding excessive rehydration. Prop patient up; give oxygen. If the pulmonary oedema is due to overhydration, stop intravenous fluids, give diuretic (frusemide 40mg intravenously) and withdraw 250ml of blood by venesection into a donor bag

^a In all cases, infusion or injection of an appropriate antimalarial drug should be started immediately

8. Shock, algid malaria Suspect Gram-negative septicaemia; take blood samples for culture. Give parenteral antimicrobials; correct haemodynamic disturbances
9. Spontaneous bleeding Transfuse fresh whole blood or clotting factors; give vitamin K injection and coagulopathy
- 10 Hyperpyrexia Use tepid sponging and fanning; give antipyretic (paracetamol 15mg/kg of body weight)
11. Hyperparasitaemia Give initial dose of parenteral antimalarial therapy. If parasitaemia in a severely ill patient exceeds 10%, carry out exchange or partial exchange transfusion
12. Malarial haemoglobinuria Continue antimalarial treatment; transfuse fresh blood to maintain haemocrit above 20%; give frusemide 20mg intravenously
13. Aspiration pneumonia Give parenteral antimicrobials; change position of patient; give physiotherapy; give oxygen.

Legends to figures

Fig 1 Acute pulmonary oedema in a pregnant woman (Copyright D A Warrell)

Fig. 2 Severe malarial anaemia in a primigravida, occurring in the 2nd trimester of her pregnancy

Fig. 3 Retinal haemorrhages in malaria (Copyright D A Warrell)

Fig. 4 Opisthotonos in a child with cerebral malaria (Copyright M E Molyneux)

Fig. 5 Prevalence of *P. malariae* in nephrotic and non-nephrotic children

Fig. 6 Prevalence of *P. malariae* in nephrotic and non-nephrotic Nigerian children (aged 2-10 years) overall *P. malariae* infection rate:

(1) Nephrotic (113) - non-nephrotic ill children
(920) $X^2 = 138.3$; $n=1$; $P. < 0.001$

(2) Nephrotic (113) - unselected "healthy" village children (340)
 $X^2 = 177.1$; $n=1$; $P. < 0.001$

No statistical difference in *P. falciparum* infection rates in the three groups was found.

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