Treatment of severe malaria

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Summary

In the treatment of severe *Plasmodium falciparum* infection antimalarial drugs should, ideally, be given by controlled rate intravenous infusion until the patient is able to swallow tablets. In cases where infection has been acquired in a chloroquine resistant area, and where it has broken through chloroquine prophylaxis or where the geographical origin or species are uncertain, quinine is the treatment of choice. When access to parenteral quinine is likely to be delayed, parenteral quinidine is an effective alternative. A loading dose of quinine is recommended in order to achieve therapeutic plasma concentrations as quickly as possible. In the case of chloroquine sensitive *P. falciparum* infection, chloroquine, which can be given safely by slow intravenous infusion, may be more rapidly effective and has fewer toxic effects than quinine. There is limited experience with parenteral administration of pyrimethamine sulphonamide combinations such as Fansidar, and resistance to these drugs has developed in South East Asia and elsewhere. Mefloquine and halofantrine cannot be given parenterally. Qinghaosu derivatives are not readily available and have not been adequately tested outside China.

Supportive treatment includes the prevention or early detection and treatment of complications, strict attention to fluid balance, provision of adequate nursing for unconscious patients and avoidance of harmful ancillary treatments. Anaemia is inevitable and out of proportion to detectable parasitaemia. Hypotension and shock ('algid malaria') are often attributable to secondary gram-negative septicaemia requiring appropriate antimicrobial therapy and haemodynamic resuscitation. Many patients with severe falciparum malaria are hypovolaemic on admission to hospital and require cautious fluid replacement. Failure to rehydrate these patients may lead to circulatory collapse, lactic acidosis, renal failure and severe hyponatraemia. However, pulmonary oedema may be precipitated by excessive fluid replacement. Hypoglycaemia can result from quinine- or quinidine-induced hyperinsulinaemia or may be associated with appropriately low plasma insulin concentrations in patients who have not yet started antimalarial chemotherapy. Young children, pregnant women and patients with severe manifestations, such as hyperparasitaemia, are at particular risk of developing hypoglycaemia. Disseminated intravascular coagulation is a relatively uncommon complication and treatable by transfusion of fresh blood or concentrates. Dexamethasone, once fashionable for the treatment of cerebral malaria, did not improve mortality when when used in a total dose of 2 mg/kg in 48 h in Thailand or 11.4 mg/kg in 48 h in Irian Jaya. In Thailand, dexamethasone treated patients remained unconscious for longer and had an increased risk of infections and gastrointestinal bleeding. Established renal failure requires peritoneal dialysis or haemodialysis which should be started early. From published evidence on 30 selected cases, it seems likely that exchange blood transfusion may lower parasitaemia more rapidly than optimal chemotherapy alone. However, the potential advantages of exchange transfusion must be balanced against the dangers, especially in the malaria endemic area. There is currently great interest in the possibility of reversing cytoadherence of parasitized erythrocytes in deep vascular beds by the use of hyperimmune serum.

Introduction

Severe malaria is nearly always caused by *Plasmodium falciparum*. However, vivax malaria may be complicated by splenic rupture, hepatic dysfunction with mild jaundice, thrombocytopenia and life-threatening or fatal anaemia. Transfusion malaria caused by *P. vivax*, *P. ovale* and *P. malariae* may, on rare occasions, be fatal if the recipient is immunocompromised or splenectomized.

Early suspicion of the diagnosis of severe falciparum malaria is of the utmost importance. Malaria must be excluded in any febrile patient who has visited the endemic area, even for a brief period, and while there has received a blood transfusion or been exposed to other rare routes of infection (transplacental, contaminated needle, marrow/tissue transplants). In Britain, almost 90% of patients with imported falciparum malaria develop symptoms within one month of leaving the endemic area[1]. Two-thirds of those with vivax or ovale malaria present within 6 months but, unusually, this may be delayed for a year or more. In the USA, 80% of falciparum and 25% of vivax cases presented within one month, and only 3% became ill one year or more after arrival[2]. Unexpected symptoms such as abdominal pain, diarrhoea or psychosis may be misleading. Common, and frequently disastrous misdiagnoses include viral encephalitis or psychosis (cerebral malaria), viral hepatitis (malarial jaundice), influenza, traveller's diarrhoea and acute renal failure of unknown cause. Clinical suspicion of severe falciparum malaria should prompt a therapeutic trial of antimalarial drugs even if parasites are not found in the blood film on several occasions as the phenomenon of 'smear negative' cerebral malaria is well recognized and delay in initiating chemotherapy is significantly related to mortality. In Britain, patients with imported malaria have died within 24 hours of becoming ill.

Criteria for the diagnosis of severe/complicated malaria are given in Table 1.

Table 1. Criteria for the diagnosis of severe/complicated malaria

Defining criteria of severe disease	*Other manifestations*
1 Cerebral malaria (unrousable coma)	1 Impaired consciousness but rousable
2 Severe normocytic anaemia	2 Prostration, extreme weakness
3 Renal failure	3 Hyperparasitaemia
4 Pulmonary oedema	4 Jaundice
5 Hypoglycaemia	5 Hyperpyrexia
6 Circulatory collapse, shock	
7 Spontaneous bleeding/ disseminated intravascular coagulation	
8 Repeated generalised convulsions	
9 Acidaemia/acidosis	
10 Malarial haemoglobinuria	

In patients presumed to be non-immune one or more major or minor criteria indicate severe disease. In endemic areas one or more major criteria or two or more minor criteria indicate severe disease

Initial procedures

Severe falciparum malaria is a medical emergency which should be managed in an intensive care unit. Weighing the patient, especially a child, is important for calculating the correct dose of antimalarial drug and to follow the overall state of hydration from day to day. Because of orthostatic hypotension, which is exaggerated by quinine, chloroquine, mefloquine and other antimalarial drugs, the patient should be kept in bed. It is useful to make a rapid initial clinical assessment, to be followed later by complete clinical examination after treatment is underway.

If there is any impairment of consciousness, the blood glucose must rapidly be checked using a 'stix' method (for example Boehringer Corporation 'BM test glycemie 20-800', 'Reflotest-hypoglycemie' and 'Reflomat'), or a test dose of intravenous glucose should be given to exclude hypoglycaemic coma. Other important laboratory measurements include parasite count, haematocrit, platelet and white cell counts, serum electrolytes, urea or creatinine, blood culture and measurement of arterial blood gas tensions, pH, bicarbonate and lactate.

Rectal temperature should be measured. Temperatures above 38.5°C can cause confusion, delirium, coma and febrile convulsions, especially in young children, and fetal distress in pregnant women. Hyperpyrexia between 39.5 and 42°C may cause permanent brain damage. Patients should therefore be cooled by removing their clothes, fanning them, and using tepid sponging, cooling blankets or antipyretic drugs such as paracetamol (15 mg/kg by mouth, suppository or by nasogastric tube).

In children with cerebral malaria, convulsions are common and associated with delayed recovery of consciousness and an increased risk of neurological sequelae and death[3]. In a double blind placebo controlled trial in Thai adults with cerebral malaria, a single low dose of phenobarbital (3.5 mg/kg) given intramuscularly on admission to hospital reduced the incidence of convulsions[4]. A larger dose (5-15 mg/kg) is probably necessary for optimal effect.

Antimalarial chemotherapy

Among patients with severe falciparum malaria in eastern Thailand, almost all the deaths occurred during the first 96 h after admission to hospital and the start of quinine treatment[5]. To have any impact on this early mortality, parenteral treatment must be started as quickly as possible using a rapidly acting schizonticidal drug to which the parasites are likely to be sensitive. From a theoretical point of view the ideal regimen would be one which achieved effective blood concentrations, above the measured *in vitro* or *in vivo* minimal inhibitory concentrations (MIC), as quickly as possible but without causing dangerous side effects. Few data

Table 2. Antimalarial chemotherapy in adults and children with severe falciparum malaria and in those who cannot swallow tablets

Chloroquine-sensitive	*Chloroquine-resistant or origin unknown*[a]
(1) *Chloroquine*: 10 mg *base*/kg in isotonic fluid by constant rate iv infusion over 8 h, followed by 15 mg/kg over 24 h	(1) *Quinine*: 7 mg dihydrochloride/kg (loading dose)[b] iv by infusion pump followed immediately by 10 mg/kg diluted in 10 ml/kg isotonic fluid by iv infusion over 4 h, repeated 8 hourly (maintenance dose) until the patient can swallow, then quinine tablets approx. 10 mg salt/kg 8 hourly to complete 7 days treatment
or (2) *Chloroquine*: 5 mg *base*/kg in isotonic fluid by constant rate iv infusion over 6 h repeated immediately every 6 h to a total dose of 25 mg *base*/kg over 30 h	or (2) *Quinine*: 20 mg/kg (loading dose) by iv infusion over 4 h, then 10 mg/kg over 4 h until patient can swallow, then quinine tablets to complete 7 days treatment
or (3) *Quidine*: (see right hand column)	or (3) *Quinidine*: 10 mg gluconate/kg (loading dose)[b] by infusion over 1-2 h, followed by 0.02 mg/kg/min by infusion pump for 72 h or until the patient can swallow, then quinine tablets to complete 7 days treatment
	or (4) *Quinidine*: 15 mg gluconate/kg (loading dose)[b] by iv infusion over 4 h, then 7.5 mg/kg over 4 h, 8 hourly until patient can swallow, then quinine tablets to complete 7 days treatment

[a]In areas of quinine-resistance (eg Thailand) add tetracycline 250 mg four times a day for 7 days except for children under 8 years and pregnant women
In patients requiring more than 48 h of parenteral therapy halve maintenance dose to 5 mg/kg
[b]Loading dose should not be used if patient received quinine or mefloquine within the preceding 12-24 h

are available to judge the clinical value of this approach or the validity of using the MIC as a target blood concentration[6,7]. Deleterious effects of rapid parasite killing, for example a Jarisch-Herxheimer reaction, have never been convincingly demonstrated, but a recent study described clinical deterioration, fever, seizures and haemolysis associated with a sudden lysis of parasitaemia on the second day of chemotherapy[8]. Treatment should be sustained long enough to ensure rapid clearance of asexual parasitaemia. In severe malaria, the use of single dose regimens to ensure compliance, the prevention of late recrudescences (RI resistance) and the destruction of gametocytes are of minor importance. Unpleasant side effects such as cinchonism (quinine, quinidine) or pruritis (chloroquine) are acceptable in the treatment of a life-threatening infection and should not limit dosage. Before starting treatment it is important to try to find out if the patient has taken an antimalarial drug within the last 24 h and if there is any past history of heart disease, cardiac arrhythmias or hypersensitivity to antimalarial drugs. Dosage must always be calculated according to body weight. The response to treatment must be carefully monitored by frequently examining the patient, recording temperature, pulse, blood pressure etc. and by repeating the blood film at least 6 hourly. As soon as the patient is able to swallow tablets, the course of treatment should be completed by the oral route.

Recommended parenteral regimens are listed in Table 2.

Quinine

Quinine is the drug of choice, unless it is certain that the infection was acquired in an area where there is no high grade resistance to chloroquine. Intravenous quinidine gluconate, widely available for the treatment of cardiac arrhythmias in some countries, is a useful alternative if parenteral quinine is not immediately available. Quinine/quinidine should never be given by intravenous 'push' or bolus injection although this is still advocated in some textbooks. Ideally, these cinchona alkaloids should be given by slow controlled rate intravenous infusion. Unless the patient has been given quinine, quinidine or mefloquine within the previous 12 h, an initial loading dose should be given to ensure that therapeutic blood concentrations are achieved as early as possible. The dose of quinine or quinidine should be halved if parenteral treatment has to be continued for more than 72 h or if the plasma concentration exceeds 15 mg/l at any stage. The 'ideal' regimen, modelled on pharmacokinetic data, involves an initial loading dose infusion of 7 mg/kg of quinine dihydrochloride given over 30 min with a constant rate infusion pump, followed by a 4 h infusion of 10 mg/kg. Thereafter, the conventional 10 mg/kg should be given over 4 h at 8 h intervals, or, in areas of relative quinine sensitivity, at 12-h intervals[9]. When the use of an infusion pump is not possible, a loading dose of 20 mg/kg of quinine dihydrochloride can be safely infused over 4 h[6]. Misunderstandings have arisen because the principle of using a loading dose has been confused with the absolute doses required in different geographical areas. Thus, in eastern Thailand, a loading dose of 20 mg/kg and a maintenance dose of 10 mg/kg 8-hourly was required to produce blood levels around the MIC of quinine for local strains of *Plasmodium falciparum*, whereas in other areas (perhaps Kenya), a loading dose of 10 mg/kg and maintenance doses of 5 mg/kg given 12-hourly might be adequate in view of the lower MICs.

Chloroquine

Chloroquine is the treatment of choice in those dwindling areas of the world where *P. falciparum* remains sensitive - currently (May 1989) Central America, the Caribbean, the Middle East and parts of West Africa. Chloroquine is recommended because it is less toxic than quinine and may be more rapidly effective. It should not be used if the infection has broken through chloroquine prophylaxis, the clinical condition does not appear to be responding to chloroquine treatment, or if there is any doubt about the origin of the infection. Some physicians may prefer to use quinine in all cases of severe falciparum malaria because of the risk of newly emergent chloroquine resistance even when the infection has been acquired in a predominantly chloroquine sensitive area of the world. Recent studies in Zambia, Thailand, Sri Lanka and the Gambia have demonstrated that chloroquine can be given safely by parenteral routes even in children with severe falciparum malaria[10-15].

Alternatives to intravenous administration

When it is not possible to give quinine or chloroquine by intravenous infusion, quinine dihydrochloride may be given by intramuscular injection[16-18]. Use of dilute solutions of quinine dihydrochloride (30 or 60 mg/ml) and adjustment to neutral pH may reduce the risk of local irritation and other side effects (White NJ, personal communication).

Resistance to quinine

Sensitivity of strains of *P. falciparum* in South East Asia and parts of Africa has been decreasing during the past few years. For infections originating in these areas, Fansidar (pyrimethamine-sulfadoxine), clindamycin or tetracycline can be added to prevent recrudescences. Tetracycline is contraindicated in pregnant women, children less than 8-years-old and patients with renal failure. Mefloquine (Lariam), recently marketed in Switzerland, France and West Germany and soon to be available in Britain, can only be given by mouth. Absorption of mefloquine suspension given by nasogastric tube to patients with cerebral malaria was rapid but unreliable in very sick patients[19]. However, severe falciparum malaria has apparently been successfully treated with oral mefloquine in a number of cases reported from France[20].

A formulation of Fansidar is available for intramuscular injection. Although the limited amount of clinical evidence suggests that it clears parasitaemia as quickly as chloroquine[21,22], theoretical concerns about the late stage of the parasite's life cycle at which the combination is active prevents its being recommended for the treatment of severe infections.

Derivatives of qinghaosu (artemisinin) have shown rapid antimalarial action in vivo and in vitro, and have proved effective in severe falciparum malaria in China[23]. Unfortunately, these promising compounds have not yet been evaluated adequately outside China and are not generally available.

Toxicity of quinine, quinidine and chloroquine

Quinine at plasma concentrations above about 5 mg/l produces 'cinchonism' - giddiness, tinnitus, high tone

deafness, tremors, blurred vision, nausea, vomiting and dysphoria; and at concentrations above 20 mg/l may cause blindness, deafness, hypotension, electrocardiographic abnormalities and central nervous system depression. Patients with malaria seem to be protected against severe toxicity, possibly as a result of increased binding by acute phase proteins. Quinidine, more than quinine, causes prolongation of the QT_c interval and QRS complex but this is rarely associated with dysrhythmia or hypotension unless the drugs are given too rapidly[24-26]. Hypoglycaemia caused by hyperinsulinaemia is the commonest important side effect of quinine and quinidine[27]. Although high doses of quinine may stimulate the uterus and have been used to induce abortion, normal therapeutic doses can be used with confidence even in the third trimester[28,29].

Chloroquine at plasma concentrations above 250 ng/ml causes dizziness, diplopia, difficulty in visual accommodation, dysphagia, nausea and vomiting. Pruritis is a common side effect in black-skinned patients. Very high plasma concentrations following parenteral administration may cause vasodilatation, hypotension, cardiotoxicity and death. Fatal hypotensive collapse has been reported in small children with severe malaria given intramuscular chloroquine especially in West Africa. These disasters were probably explained by transiently very high plasma concentrations of the drug during its distribution phase, following rapid absorption in febrile vasodilated patients[10]. Severe chloroquine toxicity can be treated with diazepam and isoprenaline in an intensive care unit[30].

Treatment of complications

Anaemia

Anaemia is an inevitable result of erythrocyte parasitization and is proportional to the intensity of parasitaemia. Where fresh, pathogen-free compatible blood is readily available, patients should be transfused when their haematocrit falls towards 20%. In patients who are fluid overloaded or have been chronically severely anaemic, exchange transfusion is a safer method of correcting the anaemia without precipitating pulmonary oedema. It is important to include the volume of transfused blood in the calculation of overall fluid input. Compatible donor erythrocytes may be very rapidly eliminated in some patients recovering from malaria; this phenomenon is not attributable to quinine mediated haemolysis[31].

Disseminated intravascular coagulation

This is commonly reported in imported cases of severe falciparum malaria in non-immune subjects. Heparin proved dangerous in this situation. The best treatment is to transfuse fresh whole blood or concentrates of clotting factors and platelets. In fluid overloaded patients exchange transfusion can be used. Vitamin K, 10 mg by slow intravenous injection, is indicated if the prothrombin or partial thromboplastin times are prolonged. Drugs which increase the risk of gastrointestinal bleeding (aspirin, corticosteroids) should be avoided in patients with severe malaria.

Hypoglycaemia

Hypoglycaemia complicates malaria in three clinical settings: in patients given quinine or quinidine, in pregnant women and in patients with severe disease, especially young children. Since hypoglycaemia may be asymptomatic[28] or its manifestations confused with other symptoms and signs in severe malaria, blood glucose must frequently be checked, especially in the high risk groups. If there is any doubt the patient should be given a therapeutic trial of intravenous 50% dextrose. In children, a continuous infusion of 5% dextrose (80 ml/kg/24 h) may prevent quinine induced hypoglycaemia[32]. However, in adults in Thailand, hypoglycaemia developed or recurred despite continuous intravenous infusions of 5 or even 10% dextrose. Glucagon is effective in a small number of cases. Intravenous 50% glucose is always effective at least temporarily, but its repeated use to treat recurrent hypoglycaemia may eventually lead to circulatory overload, rebound hyperinsulinaemia, hypokalaemia and acidosis. Glucose may be given by nasogastric tube to unconscious patients, or by peritoneal dialysis in those undergoing this treatment for renal failure. Among agents which block insulin release, diazoxide was ineffective, but the somatostatin analogue SMS 201-995 effectively blocked quinine induced hyperinsulinaemia when given by continuous intravenous infusion by pump[33] or, more conveniently, by a single subcutaneous injection (Phillips *et al.*, unpublished). This therapeutic approach is particularly attractive in patients who are severely hypoglycaemic but fluid overloaded and in whom repeated injections of hypotonic solution might precipitate pulmonary oedema.

Cerebral malaria

Patients with cerebral malaria, the commonest manifestation of severe falciparum malaria, require expert nursing care in an intensive care unit, as they are unconscious and liable to convulsions, vomiting, aspiration pneumonia and other complications of prolonged immobility. They should be turned at least every 2 hours. Level of consciousness (graded according to the Glasgow Coma Scale)[34], pulse, blood pressure, temperature, central venous pressure, urine output, fits and other new signs should be recorded frequently. Results of recent studies of the pathophysiology of cerebral malaria in humans have generally been in support of the mechanical hypothesis[35]. Cerebral oedema appears to be very uncommon except as a terminal phenomenon or in severely ill patients who have been ventilated and dialysed[36]. A number of potentially harmful remedies, based on outmoded hypotheses of unproven value, have been recommended for the treatment of cerebral malaria (Table 3). Corticosteroids, especially dexamethasone, had been fashionable since the 1960s in the hope that their proven anti-inflammatory action would reduce putative cerebral

Table 3. Cerebral malaria: ancillary treatments of unproven efficacy

Corticosteroids (dexamethasone)
Other anti-inflammatory agents (chloroquine)
Other brain-shrinking agents (urea, mannitol, invert sugar)
Low molecular weight dextran
Adrenaline
Heparin
Prostacyclin
Oxypentifylline (Trental)
Hyperbaric oxygen
Cyclosporin A
Hyperimmune serum

oedema. Two double blind placebo controlled studies have been carried out in patients with cerebral malaria, testing a moderate dose (approximately 2 mg/kg) and a high dose (approximately 11 mg/kg) of dexamethasone given by intravenous injection over 48 h.[37,38] Neither demonstrated improvement in mortality. Both studies have been criticised on various grounds,[39-41] but the serious side effects demonstrated in these studies (prolonged unconsciousness, gastrointestinal bleeding and increased incidence of secondary bacterial infections) were not balanced by an improvement in mortality; thus, the use of these drugs seems no longer justified. Similar side effects have been observed during recent studies of high dose corticosteroids used in septicaemic shock and intracerebral haemorrhage[42-44] . Corticosteroids have also been suggested for the treatment of haemolysis, blackwater fever, algid malaria, thrombocytopenia and pulmonary oedema, but no benefit has been proved. Other osmotic or diuretic agents, such as mannitol and urea with invert sugar, aimed at reducing cerebral oedema, have not been proved to be beneficial and carry the risk of producing electrolyte disturbances and circulatory overload[45]. Low molecular weight dextrans can reduce blood viscosity, but this effect is redundant in patients with severe malaria whose blood viscosity is already reduced because of the inevitable anaemia. Dextrans are contraindicated in patients with thrombocytopenia and bleeding diatheses. More information is needed about the effects of prostacyclin and its synthetic analogues which have been used in a few patients with severe malaria[46].

Disturbances of fluid electrolyte and acid base balance

Even in temperate climates, patients with severe falciparum malaria may become dehydrated through failure to drink, increased insensible losses during high fever, and in some cases profuse vomiting and diarrhoea. The resulting hypovolaemia will be manifested clinically as postural hypotension, low central venous pressure, reduced ocular tension and tissue turgor and reduced urine volume with high specific gravity. Associated abnormalities include hyponatraemia and hypoalbuminaemia. Relative or functional hypovolaemia may exist despite increased blood or plasma volume and normal total body water and extracellular fluid volume[47-49]. Failure to rehydrate such patients may result in hypotension, shock, inadequate tissue perfusion, lactic acidosis and renal failure. However, excessive fluid replacement, together with hypoalbuminaemia and possibly neutrophil mediated pulmonary capillary damage, may cause pulmonary oedema. Because of the danger of precipitating fatal pulmonary oedema, rehydration must be cautious and take into account the volume of transfused blood and the volume of fluid used as a vehicle for intravenous infusion of antimalarial and other drugs. Only isotonic fluid should be used. Urine output and specific gravity must be recorded and fluid balance checked against the daily weight. If the jugular venous pressure is difficult to see, a central venous catheter should be introduced. Impending *pulmonary oedema* is announced by respiratory distress, tachypnoea and basal crepitations with or without a rise in central venous or pulmonary artery wedge pressure. The differential diagnosis includes aspiration pneumonia and metabolic acidosis which may be distinguished by chest radiography.

Treatment of the two types of pulmonary oedema is different. Patients with normal or low pulmonary wedge pressures resemble those with adult respiratory distress syndrome and should be treated by mechanical ventilation with positive end expiratory pressure. Patients with high pulmonary wedge pressures should be given potent intravenous diuretics, venesected or 'physiologically venesected' by inflation of cuffs on the limbs or treated with vasodilators such as isosorbide dinitrate or sodium nitroprusside.

Renal failure

In Thailand, about a third of the adult patients with cerebral malaria showed elevations in blood urea nitrogen and serum creatinine concentrations. The majority of these patients were clinically hypovolaemic. Urine output was restored by cautious infusion of isotonic saline, without allowing the central venous pressure to rise above +5 cm. Patients refractory to this treatment were given increasing doses of slowly infused intravenous frusemide (up to a total dose of 1 g) and finally an infusion of dopamine (2.5-5 μg/kg/min) into a central vein. If these measures failed to achieve a sustained increase in urine output, strict fluid balance was enforced and the patients were treated with peritoneal dialysis. Indications included hyperkalaemia, fluid load, metabolic acidosis and clinical manifestations of uraemia. Haemodialysis and haemofiltration have been used successfully and have theoretical advantages over peritoneal dialysis in severe malaria. The initial doses of antimalarial drugs should not be reduced in patients with renal failure, but maintenance doses may need to be reduced after 24 h of treatment. In blackwater fever, the kidney may be damaged by passage of the products of massive intravascular haemolysis. Some nephrologists favour the use of mannitol and bicarbonate, as in the treatment of myoglobinuria[45].

Lactic acidosis in severe malaria may result from impaired tissue perfusion caused by microvascular obstruction by parasitized erythrocytes, hypovolaemia, and reduced hepatic clearance of lactate. Treatment should be aimed at improving perfusion and oxygenation by correcting hypovolaemia, clearing the airway, increasing inspired oxygen concentration and treating septicaemia, a frequently associated complication. Dichloroacetate, which stimulates pyruvate dehydrogenase principally in skeletal muscle, has been suggested for the treatment of lactic acidosis[50]. Severe acidosis (arterial pH less than 7.2) can be treated by cautious infusion of sodium bicarbonate or Tris (hydroxymethyl)-aminomethan. Hypotension and shock may develop in severe malaria as a result of pulmonary oedema, massive gastrointestinal haemorrhage, splenic rupture or uncorrected gross dehydration. Some patients are hypotensive with cold, clammy, cyanosed extremities conforming to the classical descriptions of 'algid malaria'. These patients are likely to be suffering from gram-negative septicaemias to which patients with severe falciparum malaria seem particularly vulnerable[37]. Haemodynamic problems should be corrected by giving plasma expanders, inotropic agents and selective vasoconstrictors such as dopamine. Appropriate 'blind' antimicrobial combinations include benzyl penicillin with cloxacillin and gentamycin or cefuroxime.

Hyperparasitaemia

In presumed non-immune patients with falciparum malaria, the mortality rises above 60% with asexual parasitaemias above half a million per microlitre (approximately 10% of erythrocytes parasitized)[51]. Since 1974, more than 30 patients have been treated by partial or complete exchange transfusion using manual methods, haemodialysers and cell separators (haemophoresis). The technique requires large volumes of blood but seems able to reduce parasite load rapidly, often with signs of clinical improvement such as recovery of consciousness and increased urine production. Exchange transfusion can correct anaemia without precipitating circulatory overload, can restore clotting factors and platelets and may remove toxic metabolites and circulating mediators and toxins. There is growing experience and confidence in this technique although no randomized controlled trial has yet been carried out[52,53].

Malaria in pregnancy

In non-immunes, falciparum malaria in the third trimester carries a bad prognosis. Uterine and fetal monitoring may reveal asymptomatic uterine contractions, fetal tachycardia and late deceleration of fetal heart rate in relation to uterine contractions indicating fetal distress[28]. Hypoglycaemia is common and may be asymptomatic. Correction of maternal hypoglycaemia may cure fetal bradycardia, and lowering maternal fever may relieve signs of fetal distress. Since placental function may be impaired and intense parasitization of the placenta may threaten the life of the mother and fetus, obstetrical advice should be obtained about possible induction of labour, the speeding up of the second stage of labour with forceps or a vacuum extractor and even Caesarean section[54]. Acute pulmonary oedema may occur before delivery and immediately after delivery with the sudden increase in peripheral vascular resistance that accompanies separation of the placenta. Fluid replacement must be strictly controlled to avoid circulatory overload in women going into labour.

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Discussion
Chairman: Professor W Peters

Dr B Walker (Department of Education & Science): With regard to Professor Warrell's comment about the unacceptable high levels of child deaths in West Africa, and perhaps impinging on the point about early treatment, I think we should recall that Ayitey-Smith and co-workers (Ayitey-Smith E, Boye GL, Nichani N, Lewis RA. Effect of hyperthermia on acute chloroquine toxicity in rabbits. *Eur J Pharmacol* 1974;**25**:201-15) suspected that the child deaths were not necessarily the consequences of late arrival of the children at the hospital but were perhaps actually due to the administered chloroquine. They thought that chloroquine toxicity may be changed in febrile conditions.

Some simple experiments were performed in which the body temperature of anaesthetized and unanaesthetized rabbits was raised in a diatherm machine to something comparable to that seen with human malarial fever. When chloroquine was then infused, the lethal dose of the drug was found to be decreased by a factor of 3. Furthermore, if the rabbits were 'heated' and then allowed to cool down again before drug infusion the chloroquine toxicity was found to be intermediate between normothermic and hyperthermic toxicity.

A regimen was then introduced in the children's ward of first bringing the temperature down as far as possible to normal by ice packs and other cooling methods, followed by a reduced dose of chloroquine. The result was a dramatic reduction in the number of child deaths.

There may perhaps be a message here when giving drug therapy to febrile patients generally.

Professor D A Warrell (Oxford): I am not sure how appropriate that model is to the febrile child with malaria. The physiological effects of external heating and fever are different. There is no need to postulate a decrease in the lethal dose of chloroquine in fever to explain the reports of sudden death after intramuscular and intravenous chloroquine, especially in African children. Because of rapid absorption of the drug in the vasodilated muscles, there are transiently high concentrations of chloroquine in the blood during the distribution phase. These can cause hypotensive collapse and death. By giving the drug by slow, controlled-rate intravenous infusion, or by *small* repeated doses intramuscularly, this problem can be prevented.