The treatment of complicated and severe malaria

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All cases of falciparum malaria are potentially severe and life threatening, especially when managed inappropriately. A major reason for progression from mild through complicated to severe disease is missed or delayed diagnosis. Once diagnosed, the priority for treatment of complicated and severe disease is the parenteral administration of adequate, safe doses of an appropriate antimalarial, in the setting of the highest possible level of clinical care (i.e. usually an intensive care unit). Supportive management of complications such as coma, convulsions, metabolic acidosis, hypoglycaemia, fluid and electrolyte disturbances, renal failure, secondary infections, bleeding disorders and anaemia is also important. The most recent advance in antimalarial chemotherapy has been the use of artesinin derivatives especially intravenous artesunate, which may well revolutionize the management of severe disease. Outside antimalarial therapy, mechanical ventilation and renal replacement have also played an important role in reducing mortality of this life-threatening condition.

Keywords: severe falciparum malaria; complicated malaria; cerebral malaria; treatment; quinine; artesinin; artesunate; artemether.

Introduction

Falciparum malaria remains a major cause of morbidity and mortality worldwide. The annual clinical caseload may well be over 500 million, leading to between 1 and 3 million deaths, mainly among young children [1]. More than 90% of these deaths occur in sub-Saharan Africa. An earlier review in this journal has dealt with the important area of the treatment of uncomplicated malaria in African children [2]. The number of cases of malaria worldwide appears to be growing because of the increasing risk of transmission in areas where malaria control has declined (e.g. India), increasing prevalence of drug-resistant strains of parasites (e.g. chloroquine resistance) and in a relatively few cases, because of increasing international travel. Whilst the majority of cases of
malaria worldwide are mild and can be treated with oral drugs, a minority, mainly because of delays in diagnosis or treatment, may develop complicated, life-threatening disease requiring parenteral therapy.

Strict World Health Organization (WHO) definitions of severe disease are essential for research purposes and allow comparison between different patient populations (Table 1) [3]. However, in clinical practice, any patient with suspected malaria who demonstrates complicated disease, i.e. prostration, any impairment of consciousness, convulsions or any manifestation of shock, decreased urinary output, respiratory distress or abnormal bleeding should be treated with parenteral rather than oral drugs. Some would argue that the non-immune patient (previously unexposed) with a *Plasmodium falciparum* peripheral parasitaemia of 2% or greater requires parenteral therapy, since deterioration can occur rapidly and sometimes unexpectedly, e.g. with convulsions and coma. Moreover, some patients because of nausea or vomiting, induced by either disease or drug(s), are unable to take by mouth and require parenteral treatment. For the purposes of this article, *complicated* malaria refers to any clinical presentation requiring parenteral treatment, whilst *severe* malaria refers to those patients whose presentation meets the strict WHO case definition of severe disease as indicated in Table 1. The treatment outlined attempts to include all cases of severe malaria in all age groups and in any clinical geographical setting. Clearly, the management will need to be tailored for the particular

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Case definitions of severe falciparum malaria [3]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral malaria</td>
<td>Unrousable coma (GCS &lt; 11/15), with peripheral <em>P. falciparum</em> parasitaemia after exclusion of other causes of encephalopathy</td>
</tr>
<tr>
<td>Severe anaemia</td>
<td>Normocytic anaemia with haemoglobin &lt;5 g dl⁻¹ (haematocrit &lt;15%) in presence of parasitaemia &gt;10 000 ml⁻¹</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>Pulmonary oedema or acute respiratory distress syndrome (ARDS) Would now also include rapid laboured ‘acidotic’ breathing sometimes abnormal in rhythm</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Urine output of less than 400 ml in 24 h (or &lt;12 ml kg⁻¹ in children) and a serum creatinine &gt;265 mmol l⁻¹ (&gt;3.0 mg dl⁻¹)</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>Whole blood glucose &lt;2.2 mmol l⁻¹ (40 mg dl⁻¹)</td>
</tr>
<tr>
<td>Circulatory collapse (shock)</td>
<td>Systolic blood pressure &lt;70 mmHg or core-skin temperature difference &gt;10°C</td>
</tr>
<tr>
<td>Coagulation failure</td>
<td>Spontaneous bleeding and/or laboratory evidence of disseminated intravascular coagulation</td>
</tr>
<tr>
<td>Complicated malaria: Impaired consciousness of any degree, Prostration, Jaundice, Intractable vomiting, Parasitaemia ≥2% in non-immune individuals (no previous malaria) Levels of parasitaemia should be interpreted in the light of immunity—see text</td>
<td>Such patients with complicated malaria should be managed as severe malaria, i.e. with parenteral antimalarials even though they do not necessarily meet the criteria of severe disease.</td>
</tr>
</tbody>
</table>
patient in a particular setting especially where diagnostic laboratories, drugs and facilities may not be available.

Clinical presentation

Of the four species of malarial parasites that commonly cause infection in man, *P. falciparum* is responsible for virtually all the severe cases and deaths. The other species, *P. vivax, P. ovale* and *P. malariae*, cause mainly a febrile illness and only rarely lead to severe disease [4]. Of all cases of falciparum malaria, around 10% can be classified as severe, among which the mortality is 10% (i.e. 1% of all cases) but may rise to as high as 50% (of case definition severe cases). Any form of complicated or severe malaria must therefore be regarded as a life-threatening medical emergency.

There are a number of common clinical patterns of severe disease in young children in endemic areas, relating mainly to age and intensity of transmission. Whereas in a highly endemic area severe anaemia occurs especially in children under 2 years of age, cerebral malaria (often with vomiting, convulsions and respiratory distress) may occur later, up to the age of 5 years in areas where the intensity of transmission may not be as high. Adults, by contrast, in either an endemic or a Western setting, more commonly develop the complications of pulmonary oedema and renal failure: these manifestations may only become evident during the course of treatment, often when parasites are disappearing from the blood. Vomiting, repeated convulsions and respiratory distress are less common in adults compared to children.

Cerebral malaria is one of the most dramatic presentations of severe falciparum malaria, but should be considered or at least anticipated in any patient with malaria, proven or suspected, in whom there is any degree of decrease in conscious level. Other neurological manifestations include increased muscle tone, brisk tendon reflexes, absent abdominal and other superficial reflexes, ankle clonus, extensor plantar responses and other features of a symmetrical upper motor neurone lesion. Retinal changes (Roth’s spots-like haemorrhages and, more rarely, oedema, exudates and papilloedema), dysconjugate gaze, clenching of the jaws and grinding of the teeth (‘bruxism’), or a brisk jaw jerk reflex may occur. Children often present with convulsions (sometimes recurrent). They may exhibit flaccid muscle tone and abnormalities of the brainstem reflexes (oculocephalic, oculovestibular, pupillary and corneal). These manifestations probably result from raised intracranial pressure which appears to be an important feature in cerebral malaria in children [5] rather than in adults. In some patients, persistent hiccoughs is a prominent but unexplained feature (personal observation). In non-endemic
areas, children with malaria are often misdiagnosed as having flu, a respiratory tract infection, infectious diarrhoea or hepatitis.

**Differential diagnosis**

Malaria must be distinguished from other febrile illnesses including viral illnesses (such as dengue fever and influenza), typhoid, brucellosis, respiratory and urinary tract infections. Less common causes of tropical fevers include visceral leishmaniasis, trypanosomiasis, rickettsial infections and relapsing fevers. The acute coma of cerebral malaria must be distinguished from viral encephalitis (herpes simplex, HIV, enteroviral, mumps, arboviral such as West Nile), bacterial meningoencephalitis (pyogenic and rarely tuberculous), fungal and protozoal meningoencephalitis (African trypanosomiasis), cerebral typhoid, brain abscess, heat stroke, cerebrovascular events, hypertensive encephalopathy, intoxications with drugs and poisons as well as other causes of coma. The renal failure of malaria must be distinguished from renal impairment due to other febrile illnesses such as leptospirosis, traditional herbal medicines, snakebite, glomerulonephritis and hypertension. The jaundice and hepatomegaly of malaria should not be confused with that of viral hepatitis (A, B and E), yellow fever, cytomegalovirus and Epstein–Barr virus infections, leptospirosis, biliary disease, drug-induced diseases and alcohol. Because cough and diarrhoea are common symptoms especially in children, malaria must not be mistaken for an upper respiratory tract infection or gastroenteritis. Malaria must be distinguished from the acute sepsis syndrome, although the two can coexist. Especially in malaria-endemic areas, malaria parasitaemia may be coincidentally present in patients with other acute pathology such as bacterial meningitis and hepatitis because such individuals after repeated bouts of malaria are able to tolerate parasites without being symptomatic, i.e. they have developed ‘anti-disease’ rather than ‘anti-parasite’ immunity.

**Diagnosis and blood film examination**

The definitive diagnosis of malaria is made by microscopic examination of both thick and thin blood films. Thick films, in which a dried drop of blood many layers thick is stained without methanol fixing and which allow the red cells but not the parasite to lyse, are sensitive at detecting especially low numbers of parasites but do not always provide the necessary fine details for species identification. Thin films, which are a monolayer of red cells dried and fixed with methanol, can provide valuable clinical information:
(i) **The intensity of infection or parasitaemia (usually measured as the percentage of red cells infected)** While parasitaemia does not always correlate with disease severity, patients with higher parasitaemias deserve special consideration for treatment with a parenteral artemisinin (e.g. artesunate), a loading dose of quinine, exchange transfusion (ET) and other urgent interventions.

(ii) **Parasite maturity** The presence of more mature ring forms, trophozoites containing pigment or schizonts in the peripheral blood film is associated with a worse prognosis than in those patients with only small immature ring forms [6].

(iii) **Neutrophils containing malarial pigment (hemozoin)** The presence of malarial pigment in peripheral blood polymorphs reflects prolonged infection and a large sequestered parasite burden. The finding of ≥5% of polymorphs containing hemozoin is associated with a poorer prognosis [7].

(iv) **Monitoring the effect of treatment** Peripheral blood films should be carefully examined at least once daily in complicated and severe malaria. An initial increase in parasitaemia is not uncommon during the first 18–24 h of treatment and paradoxically, may be of favourable prognostic significance [8]. Such a rise should not necessarily be interpreted as treatment failure leading to a change of antimalarial therapy, nor should it on its own serve as an indication for ET.

More recently, antigen capture tests [9] have been developed, but they have not yet displaced careful examination of a thin film as the ‘gold standard’ method of diagnosis, especially in cases of severe disease. The value of these tests is to exclude the possibility of malaria, more often in the case of mild disease.

**Management**

Any patient with complicated or severe falciparum malaria must be considered as a medical emergency and managed at the highest possible level of clinical care appropriate to the clinical setting, often an intensive therapy unit (ITU) [10–13].

**Investigations**

Venous access should be obtained and bloods taken for the investigations as shown in Table 2. Commonly omitted investigations include glucose, lactate, calcium, magnesium, phosphate, creatine kinase, arterial blood gases and blood cultures. These should be carried out wherever practically possible. In patients with impaired consciousness, other causes of encephalopathy should be excluded. If a lumbar puncture
Table 2 Investigations relevant in the management of malaria

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Relevance</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood film for malaria parasites</td>
<td>Essential for diagnosis—assists in assessment of severity and prognosis</td>
<td>See text</td>
</tr>
<tr>
<td>Full blood count:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>Often not anaemic on presentation. An indicator of duration of infection</td>
<td>Generally threshold for transfusion is high, e.g. &lt;7.0 gms dl(^{-1}) in adults, lower in children in an endemic area Self-recovery generally rapid once parasites cleared</td>
</tr>
<tr>
<td>White blood cells</td>
<td>Normal in uncomplicated cases. Often lymphopenic. In severe malaria often neutrophil leucocytosis</td>
<td>Generally none. When neutrophil leucocytosis present raises possibility of secondary bacterial infection [41]</td>
</tr>
<tr>
<td>Platelets</td>
<td>Usually low. Bleeding in absence of DIC uncommon except for petechiae/purpura</td>
<td>In absence of overt bleeding and platelets &gt; 10 (\times) 10(^9) (\mu)l(^{-1}) no need for platelet replacement</td>
</tr>
<tr>
<td>Blood film and parasite count</td>
<td>More mature forms, [6] pigment in (\geq)5% neutrophils or peripheral schizontaemia indicates poor prognosis [7]</td>
<td>Essential for diagnosis and continuing management if high Depending on facilities and severity might require exchange transfusion [47]</td>
</tr>
<tr>
<td>Electrolytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>Often low. Usually salt-depleted or dilutional. Some cases due to syndrome of inappropriate anti diuretic hormone secretion, cerebral salt-wasting or the inability to secrete free water</td>
<td>Usually self correcting with treatment</td>
</tr>
<tr>
<td>Potassium</td>
<td>Normal unless high in presence of acute renal failure</td>
<td>Dialysis may be necessary especially in oliguric or anuric renal failure</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Normal or high</td>
<td>Dialysis may be necessary May need replacement especially if prolongation of QTc on ECG</td>
</tr>
<tr>
<td>Calcium</td>
<td>Often low in severe cases</td>
<td>May need replacement especially if prolongation of QTc on ECG</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Can be low</td>
<td></td>
</tr>
<tr>
<td>Glucose and lactate:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>Often low in severe cases in children, also during quinine administration to adults [16]. Often absence of classical symptoms and signs of hypoglycaemia</td>
<td>Regular monitoring of glucose in severe cases especially during quinine infusion. Immediate administration of 50 mls 50% glucose then 10% dextrose Important to ensure good tissue and perfusion by adequate hydration, blood and in some cases ventilation</td>
</tr>
<tr>
<td>Lactate</td>
<td>Raised in severe cases. Good prognostic and progress marker from hour to hour. Important to measure CSF lactate if LP performed</td>
<td>Might require fresh frozen plasma and/or platelets if clinical evidence of bleeding and platelets below 10 (\times) 10(^9) (\mu)l(^{-1}) Does not require correction unless clinically relevant. Danger of fluid overload and pulmonary oedema May require reduction of quinine dosage as drug is about 80% cleared by the liver</td>
</tr>
</tbody>
</table>

(Continued on next page)
is required to confirm or refute the diagnosis of meningitis or encephalitis, the patient should be treated empirically and the lumbar puncture delayed until the patient is stable rather than risk the complications of raised intracranial pressure. HIV co-infection must be excluded early on, where appropriate. Hypoglycaemia must be excluded by bedside measurement of blood glucose and corrected promptly. The level of consciousness should be recorded frequently, using the Glasgow Coma Score (GCS) in adults and the Blantyre Coma Score in children [3].

The state of hydration must be carefully assessed. Patients with complicated and severe malaria, especially children, may be dehydrated and hypovolaemic to some degree as a result of fever, sweating, vomiting, diarrhoea and lack of fluid intake [14]. Hypovolaemia will exaggerate shock, renal impairment and lactic acidosis. However, rehydration needs to be carried out carefully especially in adults, as overhydration can induce pulmonary oedema. All unconscious patients should have a urinary catheter to accurately measure urine output.

### Table 2 (continued)

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Relevance</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transaminases</td>
<td>Can be moderately raised. If very high consider other concomitant infections e.g. hepatitis A, B, C or E</td>
<td>May require reduction of quinine dosage as drug is about 80% cleared by the liver</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Not raised in malaria</td>
<td>If raised think of other causes</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>Indicates skeletal muscle damage</td>
<td>Should pre-empt monitoring and management strategies aimed at preserving renal function including renal dialysis</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>Raised in acute attack</td>
<td>Useful for daily monitoring in severe cases</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>Raised</td>
<td>Correlates with parasite density</td>
</tr>
<tr>
<td>Blood gases:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>Acidosis important in prognosis of severe cases [34]</td>
<td>Requires adequate fluid replacement, possible blood transfusion in anemic cases and avoidance (if possible) of adrenaline if inotropes are required</td>
</tr>
<tr>
<td>PO₂</td>
<td>Hypoxia uncommon unless pulmonary oedema/infection present</td>
<td>Oxygen or ventilation</td>
</tr>
<tr>
<td>PCO₂</td>
<td>Can be low in presence of acidosis</td>
<td>Replacement unlikely to help in acidemia. May need dialysis against a bicarbonate-containing buffer [36]</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>Low in acidosis</td>
<td></td>
</tr>
<tr>
<td>Others:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinine levels</td>
<td>Free rather than total quinine levels relevant to efficacy and toxicity. α1-Acid Glycoprotein (α1-AGP) is the main quinine binding plasma protein</td>
<td>Total quinine levels not generally helpful in management. Maintain between 10–15 mg l⁻¹ according to parasite sensitivity. For quinidine (4–6 mg l⁻¹)</td>
</tr>
</tbody>
</table>
Antimalarials

All patients with any form of complicated or severe disease should be treated parenterally. Gastrointestinal absorption of drugs is variable and the drugs themselves may induce vomiting. Whilst there are no specific studies that have been carried out to establish a threshold for parenteral treatment, any patient considered to have complicated malaria (which in non-immune individuals may include parasitaemia as low as 2%) should be treated parenterally. Clearly, this may not be regarded as necessary, feasible or even practical in an endemic malarial area where the threshold for severe disease and parasitaemia may be set higher, e.g. 5% or on a clinical basis. The choice of drugs, according to availability and licensing, lies between the cinchona alkaloids, i.e. quinine or quinidine (in the USA), or one of the artemisinin derivatives, preferably intravenous artesunate (Table 3).

Quinine

Since the advent of chloroquine resistance, quinine has been the drug of choice for the parenteral treatment of malaria, but the pendulum is slowly swinging in favour of the water-soluble artemisinin derivative, artesunate. Quinine is given by slow intravenous infusion but in an emergency may be given intramuscularly in split doses as has been done in children [15]. In most cases, where patients are young and otherwise healthy, a loading dose of 20 mg kg\(^{-1}\) of quinine dihydrochloride is recommended [16]. To achieve and maintain therapeutic blood quinine concentrations safely and rapidly, an alternative consecutive-infusion regimen (7 mg of salt per kg of body weight over 30 min followed by 10 mg of salt per kg of body weight over 4 h) based on pharmacokinetic parameters in cerebral malaria has been suggested for use on an ITU (Table 3) [17]. Because cinchona alkaloids, both quinine and quinidine, are potent stimulants of insulin secretion, glucose should be carefully monitored especially in pregnant women [18].

Particularly in the elderly and those with underlying cardiovascular disease, quinine may induce life-threatening cardiac arrhythmias [19]. In younger otherwise healthy patients in endemic areas, arrhythmias appear not to be a problem [20]. This may be due to the difference in binding kinetics of quinine to \(\alpha_1\)-acidglycoprotein (orosomucoid), the main quinine-binding protein in plasma, leading to excessively high levels of free drug, responsible not only for the antiparasitic but also for the toxic effects. There are good theoretical arguments for the loading dose especially when wishing to attain therapeutic, parasiticidal drug concentrations as rapidly as possible in the face of a rapidly evolving and potentially fatal infection.
### Table 3 Antimalarial treatment regimens in severe malaria

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinine dihydrochloride</td>
<td>10 mg (salt) kg(^{-1}) by infusion over 4 h in 500 mls 5% dextrose, every 8 h until parasites less than 1% and the patient can take by mouth, then quinine sulphate 600 mg three times a day orally until parasites have cleared, then doxycycline 200 mg daily orally for 7 days</td>
<td>Can induce hypoglycaemia and cardiac arrhythmias. A loading dose 20 mg over 4 h in 500 mls 5% dextrose should be given to young otherwise healthy patients and where hyperparasitaemia cannot be treated by exchange transfusion. Special caution should be taken when used in the elderly and those with underlying cardiovascular disease. The loading dose should not be given to patients who have received quinine, quinidine or mefloquine in the previous 24 h.</td>
</tr>
<tr>
<td>Quinine dihydrochloride</td>
<td>7 mg (salt) per kg by infusion pump over 30 min followed immediately by 10 mg kg(^{-1}) over 4 h in 5% dextrose every 8 h until the parasitaemia is less than 1% and the patient can take by mouth- then quinine sulphate 600 mg three times a day orally until parasites have cleared, then doxycycline 200 mg daily orally for 7 days</td>
<td>As above</td>
</tr>
<tr>
<td>Quinidine gluconate</td>
<td>24 mg quinidine salt per kg (equivalent to 15 mg kg(^{-1}) base) infused over 4 h followed by 12 mg kg(^{-1}) salt (7.5 mg base) over 4 h every 8-hourly until parasites less than 1% and the patient can take by mouth. Then quinine sulphate 600 mg three times a day orally until parasites have cleared, then doxycycline 200 mg daily orally for 7 days</td>
<td>In an emergency and in the USA where quinine may not always be available. The same precautions as outlined above with quinine apply.</td>
</tr>
<tr>
<td>Quinidine gluconate</td>
<td>10 mg kg(^{-1}) salt (equivalent to 6.25 mg base per kg) infused over 2 h followed by a continuous infusion of 0.02 mg kg(^{-1})/min(^{-1}) salt (0.0125 mg base kg(^{-1}) min(^{-1}) quinidine) until parasites less than 1% and the patient can take by mouth. Then quinine sulphate 600 mg three times a day orally until parasites have cleared, then doxycycline 200 mg daily orally for 7 days</td>
<td>In an emergency and in the USA where quinine may not always be available. The same precautions as outlined above with quinine apply.</td>
</tr>
<tr>
<td>Artesunate</td>
<td>2.4 mg kg(^{-1}) intravenously followed at the same dose at 12 and 24 h; then once daily (usual adult dose 120 mg daily for 6 days) until patient able to take artesunate (2 mg kg(^{-1}) per day by mouth) to complete 7 days [27]. Then doxycycline 200 mg or clindamycin daily by mouth for 7 days</td>
<td>Can be given intravenously as it is water-soluble. Also requires doxycycline as recrudescences are common</td>
</tr>
<tr>
<td>Artemether [qinghaosu]</td>
<td>3.2 mg kg(^{-1}) intramuscularly on the first day, followed by 1.6 mg kg(^{-1}) daily (usual adult dose 160 mg followed by 80 mg daily for 6 days) until parasites cleared and the patient can take by mouth. Then doxycycline 200 mg or clindamycin daily orally for 7 days</td>
<td>Alternative to quinine. Usually intramuscular. Requires doxycycline as recrudescences are common</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>200 mg daily orally for 7 days (Adult)</td>
<td>To be used in conjunction with quinine/quinidine after parasite clearance and the patient can take by mouth</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>450 mg three times a day orally for 7 days (Adult)</td>
<td>To be used in conjunction with quinine/quinidine after parasite clearance and the patient can take by mouth</td>
</tr>
</tbody>
</table>
Quinidine gluconate is used in the USA where quinine is unavailable (Table 3) [21]. The recommended dose is 10 mg kg\(^{-1}\) salt (equivalent to 6.25 mg kg\(^{-1}\) base) infused over 2 h followed by a continuous infusion of 0.02 mg kg\(^{-1}\) min\(^{-1}\) salt (0.0125 mg kg\(^{-1}\) min\(^{-1}\) quinidine base). An alternative regimen involves 8-hourly intravenous infusions (Table 3).

Once the parasitaemia is less than 1% and the patient is able to take drugs by mouth, treatment may be completed with oral quinine at a dose of 10 mg salt per kg (usually 600 mg every 8 h). Quinine should be given for a minimum of five days and can be stopped thereafter once the patient is aparasitaemic for two consecutive blood films, taken 24 h apart; however, it is essential to complete the treatment with a course of oral doxycycline 200 mg daily for 7 days or, in pregnant women and children, clindamycin 20 mg kg\(^{-1}\) base per day in three divided doses (usual dose in adults 450 mg three times a day) for 7 days [22]. These drugs will prevent recrudescent infection which is common after mono-therapy with quinine. Sulphadoxine/pyrimethamine (Fansidar®) is no longer recommended because of increasing resistance. Some clinicians prefer to continue with quinine for a full seven days but this is often poorly tolerated, leading to symptoms of cinchonism (tinnitus, deafness, nausea, vomiting, ataxia and blurring of vision). In any event, even after a 7-day course of quinine without a tetracycline, recrudescence may still occur.

**Artemisinin and its derivatives**

Artemisinin derivatives are increasingly being used in the treatment of malaria of all degrees of severity. Artemisinins, especially artesunate and artemether, result in more rapid parasite clearance (being active on the immature parasite forms [23]) and are safer and simpler to administer. However, until now, this has not translated into significantly improved clinical outcome, although the results, largely using artemether, have generally favoured the artemisinins [24]. In many developed countries, artemisinin derivatives are not licensed and can only be used on a named-patient basis. However, the toxicity profile favours the use of artemisinins in complicated and severe disease and they can be used as second-line drugs in settings where quinine or quinidine toxicity preclude the use of the cinchona alkaloids, e.g. in cinchona alkaloid-induced hypoglycaemia or in cardiac arrhythmias. The more readily controlled intravenous route of administration of water-soluble artemether would favour its use above the intramuscular oil-based formulation of artemether [25] and produces a far more reliable and consistent pharmacokinetic profile [26]. Artesunate given as a bolus certainly has advantages over quinine which has a narrow therapeutic index, which
needs to be given cautiously over 4 h, demanding of nursing time, and which requires monitoring of both glycaemic state and cardiac rhythm.

The use of artesunate rather than quinine has been the only recent intervention proven to improve the outcome in severe malaria. Intravenous artesunate has been shown to significantly reduce mortality in adults by over a third (35%) in complicated and severe malaria when compared to intravenous quinine (15% as opposed to 22%) \( (P = 0.0002) \). Artesunate resulted in fewer episodes of hypoglycaemia than quinine \( [27] \). The number needed to treat to save one life ranged from 11 to 20. Reassuringly, the effects of artesunate were greatest in patients with hyperparasitaemia. Artesunate, where available, should therefore be used as the treatment of choice for severe malaria in adults. Unfortunately, the drug is not as yet widely available for parenteral administration, nor is it manufactured to Good Manufacturing Practices standards (GMP). Thus the prescriber has to take responsibility for the product administered. Artesunate has a limited shelf life. The dose is 2.4 mg kg\(^{-1}\) given intravenously, followed by the same dose at 12 and 24 h, then once daily until the patient is able to take artesunate (2 mg kg\(^{-1}\) per day) by mouth to complete 7 days, then doxycycline 200 mg or clindamycin daily by mouth for 7 days.

**Management of other manifestations**

Administration of an antimalarial drug is the only intervention of proven efficacy in severe malaria. However, other supportive measures as in many other severe systemic infections remain important.

**Cerebral malaria**

Unroutable coma may persist for up to 72 h in children and longer in adults. Long-term neurological sequelae of cerebral malaria have been reported in African children and also in non-immune travellers. These include focal epilepsy, memory impairment and diffuse white matter damage detected by magnetic resonance imaging \( [28] \). Patients who are unconscious should be nursed in the appropriate position, their stomach drained with a nasogastric tube with an endotracheal tube inserted. Regular neurological observations should be recorded. Mechanical ventilation may be necessary to reduce intracranial pressure.

There is no indication for the use of glucocorticoids in cerebral malaria. In two well-conducted studies, dexamethasone not only failed to improve case fatality of cerebral malaria but also lengthened the period of unconsciousness and the risk of infection and gastrointestinal bleeding \( [29,30] \). The value of corticosteroids in acute respiratory distress
syndrome (ARDS) or in severe Coombs’-positive anaemia due to malaria has not been explored.

In children with cerebral malaria and evidence of raised intracranial pressure [5], mannitol (1 g kg\(^{-1}\) infused over 30 min as a 10 or 20% solution) has been shown to control intermediate intracranial hypertension, but not when severe (>40 mmHg) [31]. Serum osmolality must be monitored if repeated doses are used. However, the use of mannitol has not as yet been systematically studied in malaria in adults.

**Convulsions**

Convulsions in malaria occur particularly in children and may be partly due to hyperpyrexia. Tepid sponging, fanning and paracetamol are effective. Aspirin is contraindicated in children because of its association with Reye’s syndrome, acidosis and gastrointestinal bleeding. The use of prophylactic phenobarbitone reduced the frequency of seizures but increased case fatality [32]. In patients with cerebral malaria, seizures must be treated promptly with a benzodiazepine such as diazepam or lorazepam, but these drugs carry the risk of respiratory depression.

**Respiratory distress**

Respiratory distress is an important complication of severe malaria in children [33], but can also accompany disease in adults. However, respiratory distress, i.e. the observation of deep laboured breathing, may be due to a number of causes, most importantly acidosis, but also infection, aspiration pneumonia, fluid overload, anaemia, acute lung injury and ARDS. Since each of these entities require a different modality of treatment, it is important that the clinician considers all these possibilities when embarking on treatment decisions for respiratory distress.

**Acidosis**

Acidosis is emerging as a major complication in severe malaria, with a multifactorial origin and a major impact on outcome [34]. Tissue hypoxia, liver dysfunction and impaired renal handling of bicarbonate all contribute. The management of acidosis involves principles of overall care with the administration of antimalarials, oxygen, fluids and electrolytes where appropriate. Intravenous bicarbonate is seldom of help and can lead to both hypernatraemia and hyperosmolarity. In severely anaemic and acidotic children, blood transfusion appears to improve acidosis by correcting the ‘oxygen debt’, as does mechanical ventilation [35].
undertaking haemofiltration in the context of acute renal failure and lactic acidosis, it would be judicious to dialyse against bicarbonate rather than the more conventional lactate-buffered dialysate [36]. Epinephrine (adrenaline) should be avoided if at all possible because, unlike other inotropic agents such as dopamine, dobutamine and norepinephrine, it increases lactate and exacerbates acidosis [37].

**Acute lung injury and ARDS**

ARDS may occur suddenly and unpredictably in malaria as in any other severe septic condition. As in the case of ARDS in other severe infections, the use of corticosteroids is unsupported by convincing evidence, although mechanical ventilation with positive end-expiratory pressure is effective in some cases.

**Hypoglycaemia**

Hypoglycaemia may be observed at presentation especially in African children and pregnant women in malaria-endemic areas. Clinical manifestations of hypoglycaemia, such as anxiety, tachypnoea, tachycardia, sweating and other autonomic signs, involuntary movements and abnormal posturing, can, all too easily, be misinterpreted as features of malaria itself rather than this common and important complication of the disease and its treatment. Quinine or quinidine-induced hyperinsulinaemic hypoglycaemia may occur in all groups of patients. Any patient with a blood glucose level below 2.2 meq l\(^{-1}\) should be treated immediately with an intravenous bolus of 50% dextrose solution, 1 ml kg\(^{-1}\), followed by a continuous infusion of 10% dextrose. However, profound hypoglycaemia can break through such treatment and meticulous surveillance of blood glucose levels using bedside reagent ‘stix’ methods should be employed during quinine infusion. Undetected hypoglycaemia can cause irreversible neurological damage. Quinine or quinidine-induced hypoglycaemia may develop late in the clinical course, when the patient seems to be recovering and parasitaemia has been eliminated. Hypoglycaemia is far less common when using the artemisinins [27]. Hypoglycaemia should be suspected in any patient who is convulsing, unconscious or whose GCS is deteriorating.

**Fluid overload**

Fluid overload is a risk especially when treating adults with malaria who are prone to developing iatrogenic pulmonary oedema. Profound
hypoalbuminaemia, the result of the catabolic effects of the acute infection, potentiates the leak of fluid into the alveolae. Fluid replacement should be meticulously monitored by observing central venous pressure. The use of albumin as replacement in severe malaria is unresolved and apart from its expense, runs the risk of fluid overload when used in adults. Overload pulmonary oedema should be treated with oxygen, potent diuretics, upright posture and, in extreme cases, by controlled venesection.

**Fluid and electrolyte disturbances**

Many patients with severe malaria become hyponatraemic. In most cases, this is attributable to salt depletion and dilution, exacerbated by the infusion of dextrose-containing solutions without saline. A few cases are due to the syndrome of inappropriate anti-diuretic hormone secretion and cerebral salt wasting syndrome (in which there is excessive natriuresis in patients with intracranial disease), whereas others are due to the inability to secrete free water. Sometimes, hyponatraemia develops suddenly and unexpectedly in the course of treatment of seemingly uncomplicated disease in the absence of hypoglycaemia or renal impairment [38]. Adequate fluid rehydration alone will usually allow correction of hyponatraemia. Hypertonic saline is not indicated. Hypocalcaemia is also a common feature of severe disease, often attributable to hypoalbuminaemia. Attention should be paid to plasma potassium, calcium, magnesium and phosphate concentrations especially when using cinchona alkaloids, which cause hyperinsulinaemia, and glucose solutions, which encourage potassium and phosphate to enter cells. Resulting electrolyte abnormalities can exacerbate cardiac arrhythmias.

**Blackwater fever**

Some patients, particularly if semi-immune, develop massive intravascular haemolysis and haemoglobinuria (‘blackwater fever’) especially when given quinine. It may also occur with the artemisinin derivatives [27]. The mechanism remains unknown. Blackwater fever in itself does not indicate severe renal impairment but more reflects the presence of massive haemolysis. In some cases, it may be associated with an underlying haemolytic tendency, e.g. glucose-6-phosphate dehydrogenase (G6PD) deficiency [39]. When associated with renal impairment, the prognosis is far worse.
Acute renal failure

Acute renal failure in malaria occurs especially in adults either as a component of severe disease with multiorgan failure and a poor prognosis, or when parasitaemia is declining (or has even been cleared). The renal failure of malaria is often nonoliguric, but in some cases may be oliguric (urine output <400 ml every 24 h) or anuric. Haemofiltration has proved superior to peritoneal dialysis [40]. In the ITU setting, haemofiltration or haemodiafiltration (the combination of haemodialysis and haemofiltration either simultaneously or sequentially) and in a few cases, haemodialysis may be required.

Secondary infection

Immunosuppression often accompanies severe malaria. Secondary bacterial infection (septicaemia, bacterial pneumonia, urinary tract infections or meningitis) can therefore occur early in severe malaria and lead to shock and multiorgan failure [41]. Common organisms include pneumococci, salmonella, *Escherichia coli* and other Gram-negative organisms. Fever blisters ('cold sores') due to *Herpes simplex* are a common accompaniment of malarial infection. There should be a low threshold for the use of broad-spectrum antibiotics, especially in the face of a rising neutrophil count, C-reactive protein and general deterioration of the patient’s condition. Hypotension may well be the prelude of secondary sepsis but may also be caused by a ruptured spleen or a massive gastrointestinal bleed.

Haemostatic disorders

In severe malaria, blood coagulation pathways are almost always activated [42], but spontaneous bleeding or disseminated intravascular coagulation (DIC) is relatively uncommon. This is particularly surprising in view of accompanying thrombocytopenia. Patients with malaria rarely bleed with platelet counts above $10 \times 10^9 \mu l^{-1}$. Aspirin and corticosteroids should be avoided lest they exaggerate this tendency. In the ITU, patients should be given a histamine-2 antagonist (e.g. intravenous cimetidine or ranitidine) to reduce the risk of gastrointestinal bleeding. If the clotting time is prolonged with overt bleeding, fresh frozen plasma and platelets may be given. Vitamin K (10 mg) can be given intravenously for three days.

Hyperparasitaemia

There is no consensus on what constitutes ‘hyperparasitaemia’. Hyperparasitaemia in itself does not necessarily have major prognostic significance
in semi-immune individuals (individuals living in an endemic area and exposed to malaria several times). The individuals with some antimalaria immunity can often tolerate high parasite counts without severe effects. However, in non-immune travellers, the parasitaemia is often an indicator of potentially severe disease [43], and levels as low as 2% may be considered in some cases as the prelude to severe disease. Parasitaemia is also an important factor when considering ET.

Anaemia

Normocytic anaemia of some degree (and sometimes severe) will almost always occur during the course of treatment of malaria and is due to a combination of haemolysis and dyserythropoiesis [44]. Once parasitaemia has cleared, there is almost always a vigorous marrow erythroid response with brisk reticulocytosis in patients who are not deficient in hematinsics (iron and folate), neither of which is due to malaria per se. For this reason, patients with malaria rarely need blood transfusion when the haemoglobin is above 7 g dl$^{-1}$.

Splenic rupture

Splenic rupture should be considered in any patient with falciparum malaria who develops abdominal pain and/or shock. Ultrasound and/or CT scanning together with a surgical opinion are essential for diagnosis and management.

Exchange transfusion

There are compelling theoretical reasons for the use of ET in malaria, an intraerythrocytic infection [45]. ET removes not only parasitized red cells but also toxic products, debris, harmful metabolites, uninfected red cells with reduced deformability and cytokines; moreover, it also corrects anaemia and acidosis. ET with fresh blood also replaces red cells, platelets and clotting factors and has been used successfully in a limited number of cases. Despite all these advantages, ET has not been shown to improve outcome in all studies. A meta-analysis of the use of ET in severe malaria could not endorse the use of this modality of treatment on a routine basis [46]. However, there were important limitations in this analysis, the most important being that patients in the exchanged group were iller than the non-exchanged controls. We have developed a practical set of indications which would consider all patients with an arbitrary parasitaemia of ≥30% as appropriate for ET [47]. This threshold could be lowered for patients
who have other manifestations of severe disease (Table 1), have underlying medical conditions and are elderly or pregnant. Erythrocytapheresis in which the red blood cell fraction is removed by apheresis and wherein the plasma, leukocyte and platelet fractions are returned to the patient has also been used to good effect in severe disease [48]. Erythrocytapheresis has advantages over ET because of speed, efficiency, haemodynamic stability and retention of plasma components such as clotting factors, but would only be available in specialized centres and lacks the advantage of ET of removing and replacing plasma. Because the apparent volume of distribution of the cinchona alkaloids is so great, neither the dose nor the frequency of dosing need be changed during ET or erythroctapheresis.

**Mechanical ventilation**

The respiratory indications for mechanical ventilation in malaria are not specifically different from other medical conditions, and include poor respiratory effort, acute pulmonary oedema, aspiration pneumonia and ARDS. Mechanical ventilation may also be used to reduce acidaemia (pH < 7.3) or raised intracranial pressure. Outside antimalarial chemotherapy, mechanical ventilation and renal replacement have probably been the two most important factors which have reduced mortality in the treatment of severe malaria where available.

**Other adjunctive therapies**

A number of adjunctive therapies such as anti-TNF agents, iron chelators (such as desferrioxamine) and dichloroacetate (which stimulates pyruvate dehydrogenase thereby reducing lactate) have been tried for severe malaria but have been disappointing. The anti-oxidant, N-acetylcysteine has been used, and has been shown to be both safe and a possible adjunctive therapy for severe malaria [10].

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**Conflict of interest statement**

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References