Review

New developments in the management of malaria in adults

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Summary

In dealing with malaria, the challenge that remains is prompt diagnosis and initiation of specific and supportive treatment. Physicians should be aware of the therapeutic and prognostic implications of life-threatening falciparum vs. non-falciparum malaria and be able to at least recognize the severe manifestations of malaria which may require an increased level of care or referral to a specialist unit. The most important new developments in managing malaria in patients are the increasing problem of drug resistance, the availability of new antimalarial agents (most notably the artemisinins) and general advances in the management of any acutely ill patient in critical care.

Introduction

There are up to 2000 cases of malaria and 10–20 deaths in the UK each year, making malaria the single-most common imported infection among travelers. These figures may seem trivial when set against the global scale of disease, reflected in the ‘two worlds of malaria’ i.e. in travelers and those living in endemic areas. Globally, two billion people living in endemic areas are at risk; up to 250 million clinical cases occur each year and over 1 million die, largely infants and young children in Africa.

However, it is essential in this age of rapid and easy international travel that practicing clinicians are at least aware of when to suspect, and also how to diagnose malaria; detailed specialist advice can then always be sought. A missed diagnosis can have fatal consequences. Advances in our understanding of the pathogenesis of the disease, the emergence of drug resistance and the availability of new anti-malarial drugs have influenced changes that have occurred in clinical management over recent years and justify the need of this article at this time.

Epidemiology

Wherever temperatures are favorable (exceeding the 16°C isotherm) and humans and the relevant Anopheles spp. mosquito vectors co-exist, there is potential for malarial transmission. Five species of malaria parasites are now known to affect humans and differ in their geographic distribution; Plasmodium falciparum most common in sub-Saharan Africa and Melanesia (Papua New Guinea and the Solomon Islands); P. vivax found mainly in Central and South America, North Africa, the Middle East and within the Indian subcontinent; P. ovale found almost exclusively in West Africa; P. malariae occurring worldwide, although mainly in Africa and finally P. knowlesi, recently documented on the island of Borneo and other parts of Southeast Asia.
Pathogenesis

The clinical symptoms and signs of malaria are produced solely by the asexual forms in the blood which invade and destroy red cells, localize in critical organs and tissues in the body, obstruct the microcirculation and release putative ‘toxins’ which induce the release of many proinflammatory cytokines leading to the classical malarial rigor.7

Clinical features

The most frequent presentation of malaria is that of a pronounced febrile illness. However, the clinical features can be extremely diverse.

Mild malaria

The incubation period for malaria is variable, but under optimal conditions may be as short as 7 days and in exceptional cases up to 20 years, as in the case of *P. malariae* infections. The majority (>90%) of *P. falciparum* infections in travelers occur within 6 weeks of leaving an endemic area. The presentation of malaria with a paroxysm including rigors is well known. There is usually a history of travel to or residence within an endemic area. Compliance with the most effective antimalarial chemoprophylaxis cannot exclude the diagnosis.

There may be a prodromal period of tiredness and aching. The features of a classical rigor of malaria are an abrupt onset of an initial ‘cold stage’ associated with dramatic shaking followed by an ensuing ‘hot stage’ with temperatures often over 40°C, during which there may be restlessness, excitability, vomiting or even convulsions. Finally, there is the sweating stage, with a fall in temperature and sometimes drowsiness. Such a paroxysm may last 6–10 h and a prolonged asymptomatic period may follow, lasting 38–42 h in the case of *P. vivax* and *P. ovale* infections and 62–66 h in *P. malariae* infections. In *P. knowlesi* infections the cycle occurs at each 24 h; in *P. falciparum* the periodicity of fever tends to be less predictable and the fever may be continuous due to the asynchrony of parasite development. Headache, cough, myalgia (flu-like symptoms), diarrhea and mild jaundice are non-specific symptoms of all malarias, whereas lymphadenopathy, pharyngitis or a rash are atypical and require an alternative explanation. Examination of a patient with mild malaria may reveal a fever, tachycardia and little else.

Severe malaria

Definitions of the clinical manifestations of severe malaria are for the standardization of clinical studies rather than clinical care and must therefore be taken in context (Table 1).8 However, these must be recognized early. For example, any degree of impairment of consciousness, prostration, jaundice, evidence of renal impairment, repeated vomiting or a parasitemia of ≥2% especially in non-immune individuals, should be taken seriously and treated with parenteral rather than oral antimalarials.9 In USA, this threshold is set higher at 5% parasitemia,10 but in our study of 482 patients with falciparum malaria, any patient with a parasitemia ≥2% was at distinct risk of WHO case-definition severe disease.11

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Manifestations of severe <em>falciparum</em> malaria8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manifestation</td>
<td>Comment</td>
</tr>
<tr>
<td>Cerebral malaria</td>
<td>Unrousable coma (GCS &lt;11/15), with peripheral <em>P. falciparum</em> parasitemia after exclusion of other causes of encephalopathy</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>Pulmonary edema or acute respiratory distress syndrome</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Whole blood glucose &lt;2.2 mmol/l (40 mg/dl)</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>Bleeding</td>
<td>Spontaneous bleeding and/or laboratory evidence of disseminated intravascular coagulation (DIC)</td>
</tr>
<tr>
<td>Renal involvement and blackwater fever</td>
<td>Urine output of less than 400 ml in 24 h (or &lt;12 ml/kg in children) and a serum creatinine &gt;265 mmol/l (&gt;3.0 mg/dl). Dark, black colored urine</td>
</tr>
<tr>
<td>Severe anemia</td>
<td>Normocytic anemia with hemoglobin &lt;5 g/dl (hematocrit &lt;15%) in presence of parasitemia &gt;10 000/ml</td>
</tr>
<tr>
<td>Impaired consciousness of any degree, prostration, jaundice, intractable vomiting, parasitemia ≥2%</td>
<td>Previously unexposed individuals with any of these manifestations should be managed as severe i.e. with parenteral antimalarials</td>
</tr>
</tbody>
</table>
Pregnant women are particularly at risk for severe disease especially hypoglycemia.

**Cerebral malaria**

In cerebral malaria the patient passes from drowsiness to coma insidiously over a few days or abruptly within 1–2 h often heralded by a convulsion. The majority have no focal neurologic signs, but occasionally cranial nerve palsies, monoplegia or hemiplegia, extensor posturing, decerebrate or decorticate rigidity, conjugate or even dysconjugate eye movements, grinding of the teeth (bruxism) or hiccoughs may occur. Some patients have typical retinal hemorrhages (Figure 1). Coma in malaria may not only be due to primary neurologic involvement (i.e. classical cerebral malaria), but may also be part of a prolonged post-ictal state or status epilepticus (especially in children) or a severe metabolic disorder such as acidosis or hypoglycemia, each requiring a different modality of management.

**Respiratory distress**

Respiratory distress is manifest by rapid labored breathing sometimes abnormal in rhythm. In children there may be intercostal recession, use of the accessory muscles and flaring of the alar nasae, making it difficult to differentiate from an acute respiratory infection. As with coma, respiratory distress in patients with malaria may be the result of a number of pathologies, each requiring different clinical interventions. Tachypnea may be the result of respiratory compensation for a profound metabolic acidosis as occurs in the majority of cases, or perhaps the result of secondary lung infection due to the immunosuppression that may accompany acute disease. Pulmonary edema leading to rapid respiration may be the consequence of hypoalbuminemia, iatrogenic fluid overload or direct alveolar capillary damage produced by parasites and neutrophils leading to vascular occlusion and the acute respiratory distress syndrome (ARDS). Air hunger could also be the result of severe anemia.

**Acidosis**

Acidosis (base excess ≤12mmol/l) or acidemia (pH < 7.3) in malaria indicates a poor prognosis and may be the result of number of causes: poor tissue perfusion, in some cases due to hypovolemia, leading to reduced oxygen delivery; lactate production by the parasite; lactate generation as a result of cytokine activity, especially TNF, in the acute phase response; reduced hepatic blood flow and therefore lactate clearance; impaired renal function and therefore acid excretion; and exogenous acids due to aspirin (salicylate) administration.

**Hypoglycemia**

The characteristic clinical manifestations of hypoglycemia may not be evident in malaria, often because the patient is already unconscious. Suspicion of this important complication is often circumstantial: on admission in children and during quinine therapy in adults, especially if pregnant. The cause of hypoglycemia is most likely multifactorial—due to depletion of glucose stores because of starvation or malnutrition, malabsorption of glucose due to decreased splanchnic blood flow, increased tissue metabolism of glucose, parasite utilization of glucose, cytokine-induced impairment of gluconeogenesis and hyperinsulinemia due to quinine therapy. Anaerobic metabolism of glucose leads to acidemia and the production of lactate. Acidemia (pH < 7.3) and hyperlactatemia (lactate > 6mmol/l) are indicators of a poor prognosis.

**Circulatory collapse (shock)**

Unlike in the sepsis syndrome, shock is relatively rare in severe malaria. In most cases the blood pressure of patients with malaria is at the lower end of the normal range, probably a result of vasodilatation and hypovolemia. Marked hypotension in a few cases may be the result of dehydration, but is
more commonly due to concomitant sepsis.\textsuperscript{16} Sepsis frequently arises from the respiratory and urinary tracts.

**Bleeding**

Despite the frequent presence of thrombocytopenia, most likely the result of diffuse sequestration of platelets,\textsuperscript{17} overt evidence of bleeding is rare in malaria. Bleeding is more likely to occur in the setting of disseminated intravascular coagulation (DIC). However, more often there is only subtle activation of the coagulation cascade with a reduction in antithrombin III concentration, an increase in thrombin–antithrombin III complexes and a reduction in factor XII and prekallikrein activities, which do not appear to be clinically significant.\textsuperscript{18}

**Renal involvement and blackwater fever**

A degree of renal impairment (often due to hypovolemia, but not always clinically evident), almost always occurs in severe malaria. Acute renal failure, which is less common, may occur in malaria both during the acute parasitemic phase, but also after parasite clearance. In addition acute renal failure in malaria may be nonoliguric. Although the urinary manifestation of blackwater fever may be dramatic, sometimes occurring in the setting of glucose-6-phosphate dehydrogenase (G6PD) deficiency or a semi-immune patient given quinine, it does not invariably lead to renal failure and appears to be considerably more benign than the classically described syndrome.\textsuperscript{19} Hyponatremia is probably the reflection of hypovolemia and is often self-correcting and paradoxically associated with a better outcome.\textsuperscript{20}

**Severe anemia**

The anemia of falciparum malaria is both complex and multifactorial. The fall in hemoglobin is often far in excess of what can be accounted for by the loss of infected red blood cells alone and by inference must therefore include uninfected cells. Major mechanisms in the pathogenesis of anemia in acute infection are those of red cell lysis by parasites, removal of uninfected cells due to antibody sensitization or other physicochemical changes as a result of increased reticuloendothelial activity particularly in organs such as the spleen.

**Differential diagnosis**

Malaria must be considered in all patients with fever or a history of fever who have visited a malaria endemic country. A travel history should now be a routine part of any consultation of a patient with a fever. Malaria is a great mimic and must enter the differential diagnosis of a number of clinical presentations. Fever due to malaria needs to be differentiated from typhoid, viral illnesses such as dengue fever and influenza, brucellosis and respiratory and urinary tract infections. Less common causes of tropical fevers include amoebic liver abscess, leishmaniasis, trypanosomiasis, rickettsial infections and relapsing fevers. The coma of cerebral malaria need to be differentiated from meningitis (including tuberculous meningitis), encephalitis, enteric fevers, trypanosomiasis, brain abscess and other causes of coma. The renal failure of malaria must be distinguished from renal impairment due to massive intravascular hemolysis seen in G6PD deficiency, sickle cell disease, leptospirosis, snake envenomation, use of traditional herbal medicines and chronic renal disease resulting from glomerulonephritis and hypertension. The jaundice and hepatomegaly of malaria must be distinguished from that of viral hepatitis (A, B and E, cytomegalovirus and Epstein–Barr virus infections), leptospirosis, yellow fever, biliary disease and drug-induced disease including alcohol. The anemia of malaria can be confused with other common causes of hemolytic anemia such as that due to the hemoglobinopathies (e.g. sickle cell disease, thalassemia), G6PD deficiency and must be differentiated from that of iron, folate or vitamin B12 deficiency.

**Diagnosis**

**Blood films**

The definitive diagnosis of malaria is made by prompt microscopic examination of thick and thin blood films. There is no need to wait for a fever peak before carrying out a blood film. In addition to the presence or absence of parasites, the species and parasite density can be determined from the blood film. Furthermore in falciparum malaria, other helpful information, often suggestive of a poorer prognosis, may be present on the film such as mature trophozoite forms, the presence of schizonts or excessive malarial pigment present in neutrophils or macrophages observed in some but not all studies.\textsuperscript{21}

**Other methods**

Malaria can be diagnosed using other methods, but each has its own drawbacks with regard to time, cost, or being non-quantitative or non-specific.
Rapid diagnostic tests (RDTs) based on antigen capture, using a monoclonal antibody to the histidine-rich protein 2 of *P. falciparum* or parasite lactate dehydrogenase (pLDH) of *P. falciparum* or *P. vivax*. They are useful in patients who have not had malaria before. RDTs require minimal expertise, but are expensive and are not quantitative.

The polymerase chain reaction (PCR) is useful for making an accurate species diagnosis and detecting low level parasitemias, but its expense, time taken and requirement for specialized equipment make it impractical.

### Treatment

Once a definitive diagnosis of malaria has been made the mainstay of treatment is the administration of specific and appropriate antimalarials.

#### Non-falciparum malaria

Malaria due to *P. vivax, P. ovale, P. malariae* or *P. knowlesi* requires a standard course of treatment with chloroquine, which usually leads to defervescence (Table 2). In resistant cases of *P. vivax*, atovaquone and proguanil, or quinine plus tetracycline, or mefloquine as for falciparum malaria can be used. In the case of *P. vivax* and *P. ovale*, malaria treatment with an 8-aminoquinoline (primaquine) is given to eradicate the exoerythrocytic forms, hypnozoites responsible for relapses. Levels of G6PD should be measured in all patients before they are given primaquine (see Table 2).

#### Falciparum malaria

**Mild falciparum malaria**

Increasing resistance to chloroquine and pyrimethamine with sulfadoxine (Fansidar) worldwide make these drugs obsolete for the treatment of falciparum malaria. A range of treatments are available depending on affordability, cost and choice of local practice (Table 3). There is increasing use of drug combinations such as atovaquone with proguanil (Malarone) and artemether with lumefantrine (Riamet), which are better tolerated than quinine. Mefloquine (Lariam) may also be used. Whichever drug is used, parasitemia may paradoxically rise in the first 24–36 h and is not generally indicative of treatment failure. Quinine requires treatment to be followed up by a second agent to prevent recrudescence.

**Severe falciparum malaria**

The management of severe falciparum malaria constitutes a medical emergency. The diagnosis needs to be confirmed microscopically and intravenous access obtained as soon as possible. Patients with severe malaria should be transferred to the highest possible level of clinical care (e.g. a high-dependency or intensive therapy unit). Extra vigilance needs to be observed in pregnancy but apart from caution if artesunate is to be used, the avoidance of doxycycline and a lower threshold for exchange transfusion, the management is no different. Measurement of glucose, and where possible, lactate and arterial blood gases, should be performed in the initial assessment. Meticulous care must be given to fluid balance as both dehydration and overhydration can occur as a result of the disease or treatment.

An effective antimalarial, ideally artesunate, should be given intravenously (Table 4). Artesunate has distinct advantages over quinine in its effectiveness and toxicity profile. In a large randomized trial, artesunate resulted in a 35% absolute reduction in mortality. Unfortunately, artesunate is not as yet manufactured to good manufacturing practice (GMP), and hence does not have a product.
licensure in Europe or Food and Drug Administration approval in the USA but can be used on a named patient basis where available in the UK and via an investigational-new-drug (IND) application from the Centre for Disease Control and Prevention (CDC) in the USA. Information on the use of artesunate in the treatment of severe malaria in pregnancy is limited.

Blood should be taken for cross-matching and coagulation studies. Before parenteral therapy with quinine, a baseline electrocardiogram should be obtained with careful observation of the rhythm and QT interval in elderly patients, particularly those with underlying heart disease, and where possible a cardiac monitor should be set up.

### Blood and exchange transfusion

Blood transfusion may be of benefit in patients who have respiratory distress and metabolic acidosis. In units with appropriate facilities, complicated hyperparasitemia may be treated with exchange transfusion. The use of exchange transfusion is controversial, but should be considered where safe blood is available for all patients in whom the parasitemia exceeds an arbitrary 30% and for those in whom parasitemia is lower, but who:

- have manifestations of severe complicated malaria
- have underlying medical complaints, such as diabetes mellitus and ischemic heart disease, (iii) are elderly, or (iv) are pregnant.

During the course of treatment useful parameters for monitoring progress should include twice-daily parasite counts, regular pH and blood gas measurements and appropriate measurement of glucose and lactate concentrations and renal function. Each patient needs to be assessed individually. During quinine infusion it is essential to monitor blood glucose carefully.

Elective ventilation needs to be considered where facilities are available, especially if there is severe acidosis, clear evidence of raised intracranial pressure or respiratory failure of any cause.

### Cerebral malaria

Antimalarials form the mainstay of treatment for cerebral malaria. A number of adjuvant therapies such as corticosteroids and heparin have been tried, but have not been shown to be effective. Some children and a few adults show evidence of raised intracranial pressure, in which case a therapeutic trial of an osmotic agent such as mannitol may be attempted.

### Acute renal failure

Dialysis or hemofiltration may be required. The indications are similar to those for any other form of renal failure. Nonoliguric renal failure may be managed conservatively.

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**Table 3** Treatment of mild falciparum malaria

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Quinine sulfate</td>
<td>10 mg (salt)/kg (usually 600 mg) 8 hourly for 3–7 days. (At a practical level when parasite clearance has been achieved for 24 h)</td>
<td>Almost all patients develop cinchonism (ringing in the ears, deafness, nausea, vomiting, etc.) and especially if they have liver or renal impairment—reduce dose to twice daily if parasite count falling.</td>
</tr>
<tr>
<td>Followed by:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxycycline or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>200 mg daily for 7 days</td>
<td>Not for children or in pregnancy</td>
</tr>
<tr>
<td></td>
<td>450 mg three times a day orally for 7 days</td>
<td>Can be used for pregnant women and in children at the appropriate dose</td>
</tr>
<tr>
<td>Atovaquone and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>proguanil (Malarone®)</td>
<td>Four tablets daily for three days (each tablet contains atovaquone 250 mg and proguanil 100 mg)</td>
<td>Better tolerated than quinine. Main side effects are gastrointestinal.</td>
</tr>
<tr>
<td>Artemether and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lumefantrine (Riamet®)</td>
<td>If weight &gt;35 kg, four tablets at 8, 24, 36 and 60 h</td>
<td>Relatively few side effects</td>
</tr>
<tr>
<td>Mefloquine (Lariam®)</td>
<td>750 mg as a single dose, repeated after 6 h</td>
<td>Contraindicated in early pregnancy and in patients with neuropsychiatric history</td>
</tr>
</tbody>
</table>
Acidosis

Adequate fluid replacement avoiding fluid overload is essential. Sodium bicarbonate has not been shown to be of any benefit and may worsen acidosis. Transfusion of anemic patients has been shown to improve severe acidosis and reduce lactate concentration in young children. Early hemodilution and ventilation may be used according to availability. The inotrope epinephrine (adrenaline) should be avoided unless absolutely necessary as it may worsen the acidosis, unlike dopamine, dobutamine and norepinephrine (noradrenaline).29
Bacterial superinfection

Bacterial superinfection is common in malaria and must be suspected, particularly if the fever remains high despite antimalarial treatment or if there is evidence of focal sepsis (e.g. respiratory or urinary tract infection).

Adjunctive therapies

Many adjunctive therapies have been tried in malaria, but few, if any, have been shown to be of benefit. The use of anti-TNF antibodies has been disappointing and corticosteroids are clearly not indicated in the treatment of acute cerebral malaria. The role of iron chelators and heparin remains unresolved as does the use of an anti-TNF agent, pentoxifylline. The role of mannitol in patients who have evidence of raised intracranial pressure, dichloroacetate in patients who have hyperlactataemia and the free radical scavenger, desferoxamine, remains unclear.

Conclusion

Malaria in its uncomplicated form remains relatively easy to treat once the diagnosis is made. The challenge in complicated and severe disease is the rapid institution of appropriate antimalarials and the highest possible level of care. For severe falciparum malaria the current drug of choice is parenteral quinine. A major current limitation is the availability of artesunate, not yet manufactured to good manufacturing practice (GMP), and hence without a product licence in Europe or Food and Drug Administration Approval in the USA. Hopefully this shortcoming will be resolved in the very near future.

Conflict of interest: None declared.

References


