

Malaria: An Update for Physicians

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KEYWORDS

• Malaria • *Plasmodium* • Travel • Antimalarials

KEY POINTS

- Malaria continues to be the most important human protozoal infection worldwide, directly causing over 2000 deaths every day and causing increased susceptibility to bacterial infection.
- Artemisins, taken orally in combination with other antimalarials in non-severe malaria and administered intravenously for severe malaria have become the gold standard treatment for *P falciparum* malaria.
- The priorities in the management of imported malaria are in prevention, early recognition and early treatment.
- The priorities in management of falciparum malaria globally are prevention of the development of full artemisinin resistance and ensuring that appropriate treatments are available to all who need them.

INTRODUCTION AND HISTORICAL PERSPECTIVE

Malaria is caused by infection with protozoan parasites of the *Plasmodium* genus, transmitted to humans by female anopheline mosquitoes. Plasmodia have adapted to a wide variety of vertebrate hosts ranging from reptiles to mammals, although with 1 notable exception, human malaria is not a zoonosis. Infections likely to represent malaria have been described since mankind began to record its experiences. The earliest accurate description of human malaria in European literature has been attributed to Celsus (25 BC TO AD 54), who described tertian and quartan periodicity of fevers in his treatise *De Medicina*. Five species are now recognized as agents of human malaria (**Table 1**), although most infections are caused by 2: *Plasmodium falciparum* and *Plasmodium vivax*. Worldwide, there are estimated to be several hundred million infections with malaria every year and the historical burden of infection has helped to shape the human genome through evolutionary pressure on genes involved in erythrocyte metabolism and structure.¹ Malaria continues to kill more than 2000 people every

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Species	Distribution	Clinical/Pathologic Details
<i>Plasmodium falciparum</i>	Widespread in tropics	Causes the most fatalities Pronounced rosetting and sequestration
<i>Plasmodium vivax</i>	Widespread in tropics and subtropics except West Africa	Relapses caused by hepatic hypnozoites Requires RBC Duffy antigen for entry into cells
<i>Plasmodium ovale</i>	Patchy in West Africa and southwest Pacific	Relapses caused by hepatic hypnozoites
<i>Plasmodium malariae</i>	Patchy, worldwide	Late recrudescence and chronic infections Nephrotic syndrome (rarely)
<i>Plasmodium knowlesi</i>	Malaysia, Indonesia and other southeast Asia	Zoonosis (macaque monkeys primary hosts) Severe disease

Abbreviation: RBC, red blood cell.

day,² with strong evidence emerging that it is also indirectly responsible for more than half of all cases of invasive bacterial disease in high-transmission settings.³

Malaria was once widespread, with ongoing transmission in the southern United States and the Mediterranean rim within the last 100 years. The Centers for Disease Control and Prevention (CDC) is located in Atlanta, Georgia, because of the high prevalence of malaria in the Mississippi basin at the time of its inception. However, by 1951, malaria was eliminated from the United States and the Global Malaria Eradication Campaign, initiated in 1955 by the Global Health Assembly, succeeded in eliminating transmission from several other countries, although not in sub-Saharan Africa or south Asia.⁴

EPIDEMIOLOGY

The current distribution of malaria covers the tropics and large parts of the subtropics (Fig. 1). World Health Organization (WHO) estimates of malaria deaths worldwide

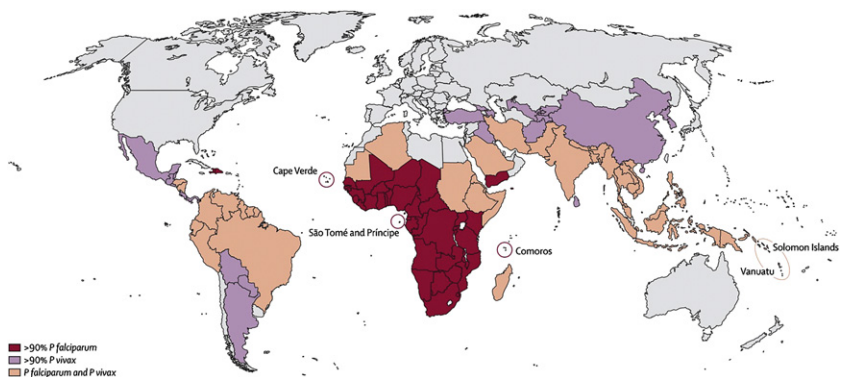


Fig. 1. Worldwide distribution of malaria. (From Feachem RG, Phillips AA, Hwang J, et al. Shrinking the malaria map: progress and prospects. *Lancet* 2010;376(9752):1570; with permission.)

decreased from 1 million in 2000 to more than 700,000 in 2009, with an estimated 756 million people at risk of the disease.² In line with these WHO data, largely derived from data supplied by National Malaria Control Programs, a summary of recent peer-reviewed publications also points to substantial reductions in malaria cases in many countries in sub-Saharan Africa, although there are difficulties in attributing this to control measures.⁵ However, there remain arguments about the accuracy of such estimates, with a recent retrospective study into malaria deaths in India suggesting that the WHO estimate for the years studied was an underestimate by a factor of 10.⁶

In the United States, the number of imported cases of malaria reported remained static between 2005 and 2009 (the last year with data available) at around 1500 cases. In 2009, of infections in which a species was identified, 74% were *P falciparum* and 18% *P vivax*, which represents a decline in the proportion of cases diagnosed with *P vivax* and a corresponding increase in those diagnosed with *P falciparum* since 2007.⁷ In the United Kingdom, there were 1762 cases reported in 2010, with 70% of cases caused by *P falciparum*.⁸ A similar reduction in the proportion of imported malaria cases caused by *P vivax* occurred in the United Kingdom between 1987 and 2006.⁹

It is increasingly recognized that there is marked variation in malaria transmission within many high-transmission regions, with foci of high transmission and lower transmission in neighboring areas.^{10–13} This variation has potential consequences for malaria control, local treatment protocols, and risk assessment for international travelers. The emergence of a new human plasmodia species, *Plasmodium knowlesi*, as a zoonosis and significant cause of infection in parts of southeast Asia has attracted significant attention.^{14,15} There may be further discoveries of zoonotic malaria as molecular techniques become more widespread.

PATHOGENESIS

The primary route of infection for all plasmodia infections is through the bite of a female anopheline mosquito. Less common routes of infection include blood transfusion of parasitized erythrocytes and congenital transmission. Following the bite of an infected mosquito, plasmodia sporozoites enter the subcutaneous tissue of the skin and migrate to local capillaries and lymphatics before passing to the liver, where they invade hepatocytes and develop into merozoites via a process of asexual reproduction known as hepatic schizogony. After a period of at least 7 days, and often longer, infected hepatocytes release tens of thousands of merozoites that each invade an erythrocyte. Having invaded an erythrocyte, each merozoite either undergoes a further round of asexual reproduction (erythrocytic schizogony) or develops into the sexual form of the malaria parasite (male and female gametocytes) (**Fig. 2**). Symptoms occur with the release of parasite toxins following the development of the blood stage of disease and are associated with asexual parasitemia.¹⁶ Gametocytes are not thought to cause symptoms, but are taken up by mosquitoes and involved in the sexual reproductive cycle within the mosquito gut.

Relapsing Malaria: P vivax and Plasmodium ovale

Unlike other human plasmodia, *P vivax* and *Plasmodium ovale* infections are characterized by relapses related to hepatic hypnozoites. A proportion of hepatocytes, infected by sporozoites from a mosquito bite, develop into dormant hypnozoites rather than into actively dividing schizonts.¹⁶ Later development of these hypnozoites into hepatic schizonts, and subsequent rupture, with the release of merozoites into the bloodstream, account for the observed relapses. Multiple, frequent relapses are characteristic of infections acquired in the tropics, whereas infections acquired in

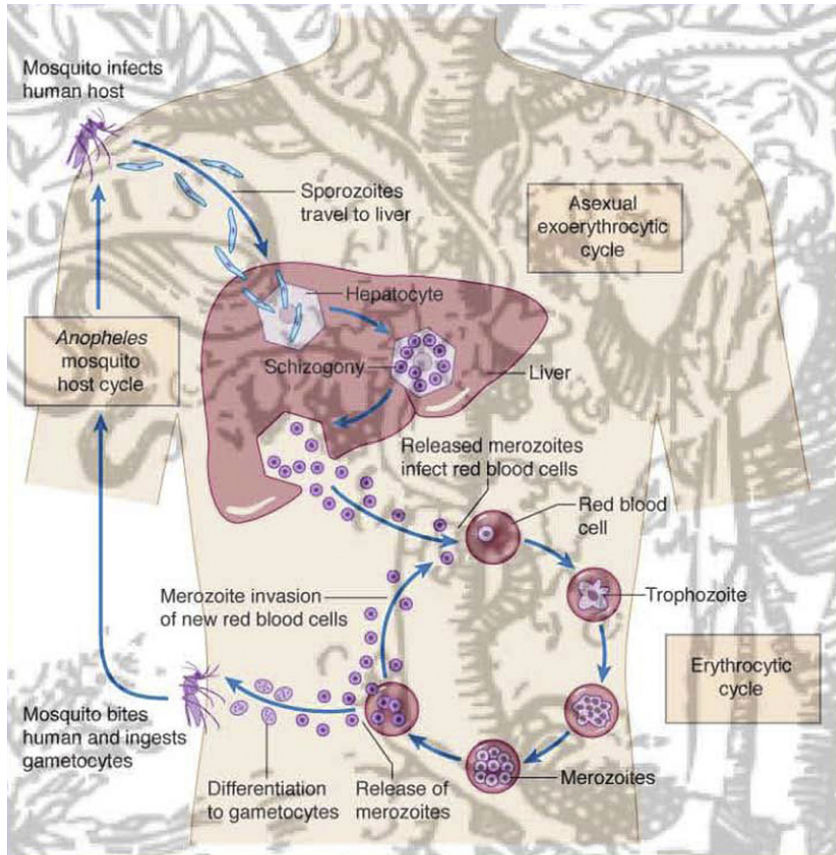


Fig. 2. The lifecycle of *Plasmodium falciparum* in the human body. (From Actor JA. Elsevier's Integrated Review: Immunology and Microbiology. 2nd edition. Philadelphia: Elsevier; 2012; with permission.)

temperate regions have less frequent relapses, often occurring some months after the initial infection. Despite attractive theories concerning adaptation to seasons or response to anopheline bites, the determinants of malaria relapse, like much of the biology of the hypnozoite, remain to a large degree a mystery and must be a priority for future research.^{17,18} Although many theories have been espoused concerning the determinants of malaria relapse, a compelling explanation proposed recently is that febrile illness (notably *P. falciparum* infection) activates latent hypnozoites.¹⁹ Given the recent data suggesting that liver-stage infection in mice is suppressed by acute *Plasmodium* infection through the hormone hepcidin,²⁰ it may be that changes in hepcidin also play a role in hypnozoite activation.

Plasmodium malariae is not associated with relapse but can cause chronic, low-grade infections that persist for years, often at levels that are less than the limits of detection by light microscopy.²¹

Pathogenesis of Severe Malaria

The nature of the pathophysiologic changes that result in severe malaria have not been completely resolved. *P. falciparum* is able to invade erythrocytes of all ages,

a characteristic it shares with *P knowlesi*,¹⁴ whereas *P vivax* and *P ovale* invade only young cells and *P malariae* older cells. This ability may contribute to the higher parasitemia seen in infections with *P falciparum* and *P knowlesi*, with the subsequent increase in virulence observed. Erythrocytes infected by midstage to late-stage *P falciparum* (trophozoites and schizonts) express the parasite-derived *P falciparum* erythrocyte membrane protein 1 (PfEMP1), which mediates both adherence to vascular endothelium (sequestration) and binding uninfected erythrocytes (rosetting).¹⁶ Together with a reduction in the deformability of both infected and uninfected erythrocytes, rosetting and sequestration result in alterations in microvascular blood flow that are a key factor in development of severe falciparum disease.²² Both rosetting and sequestration seem to occur at reduced magnitude in non-falciparum malaria,²³ and red cell deformability may be increased in erythrocytes infected with *P vivax*.²⁴ Although it is tempting to blame the pathogenesis of severe falciparum malaria entirely on microcirculatory disturbance, it is likely that multiple factors are involved, including dyserythropoiesis, erythrocyte hemolysis, and both local and systemic cytokine effects.¹⁶

CLINICAL FEATURES

In European and North America, more than 95% of malaria infections occur in travelers, often within the first month of return.²⁵ Delay in developing illness has been associated with the use of appropriate antimalarial prophylaxis, and clinicians seeing returning travelers should be aware of this possibility.²⁶ Presentation is nonspecific and may mimic other diseases including influenza, septicemia, gastroenteritis, and viral syndromes. A high index of suspicion is required, usually triggered by a travel history. Long delays and misdiagnosis in the management of malaria have been reported from studies in Europe²⁷ and North America,^{28,29} highlighting the critical importance of a travel history in all patients presenting with fever or history of fever.

If a travel history is unavailable, factors that may suggest malaria include splenomegaly, fever without localizing signs, thrombocytopenia, hyperbilirubinemia and a normal peripheral blood leukocyte count.³⁰ A recordable fever may be absent on presentation in around one-third of patients. Because falciparum malaria can progress rapidly if untreated, it is recommended that family physicians refer all suspected cases of malaria to a facility that can provide a rapid diagnosis and instigate treatment without delay.

In highly endemic countries, where infection in childhood is common and repeated infection results in an immune tolerance of malaria parasitemia, differentiating malaria from bacterial disease can be difficult. In these settings, coinfection is common, often making treatment of both necessary.^{31–33}

Severe Malaria

The WHO defines severe malaria by the presence of any 1 of several clinical or laboratory criteria in a patient with *P falciparum* asexual parasitemia and no other obvious cause (**Box 1**).³⁴ Even in trial conditions, the mortality among children with severe malaria in sub-Saharan Africa is between 10% and 15%, and in adults in Asia 15% to 20%,^{35,36} whereas the mortality among adult admissions to intensive care in European centers has been reported as 8% to 10%.^{37,38}

Severe non-falciparum malaria does occur, and in some specific locations in Asia it is increasingly being recognized as a major cause of severe malaria.^{14,15,39} Among returning travelers to the United States in 2009, non-falciparum malaria accounted for 14% of cases presenting with signs of severe disease, although this figure was lower in European data.^{7,40} Case fatality rates for non-falciparum malaria are much lower in all settings.

Box 1**Criteria for severe malaria (WHO 2010)***Clinical*

Impaired consciousness or unrousable coma

Prostration (inability to walk/sit/feed)

Multiple convulsions

Respiratory distress/acidotic breathing

Circulatory shock

Jaundice with other vital organ dysfunction

Abnormal bleeding

Hemoglobinuria

Laboratory

Metabolic acidosis (plasma bicarbonate <15 mmol/L or lactate >5 mmol/L)

Hypoglycemia

Severe anemia (hemoglobin <5 g/dL or packed cell volume <15%)

Hemoglobinuria

Renal impairment (serum creatinine >265 μ mol/L)

Hyperparasitemia (>2%)

DIAGNOSIS

Once malaria is suspected, it is usually straightforward to diagnose. Commonly used diagnostics include thick and thin Giemsa-stained blood smears and immunochromatographic rapid diagnostic tests (RDTs) of malaria antigens, both of which are in widespread use.^{41,42} In expert centers, light microscopy can detect as few as 50 parasites/ μ L (approx 0.001%), increasing to around 500/ μ L in routine settings. Sensitivity for RDTs decreases with parasitemias less than 100/ μ L for *P falciparum*, with lower sensitivity for non-falciparum malaria.⁴³ RDTs have several drawbacks; they are unable to provide a quantification of parasitemia, they perform poorly with non-falciparum malaria, and tests based on the detection of histidine rich protein 2 (HRP2) may remain positive for several weeks after malaria has been treated.

Diagnosis needs to be prompt to enable immediate treatment of falciparum disease, which can progress rapidly if untreated.⁴⁴ Despite the ability to detect parasites at a lower density than either light microscopy or RDTs, PCR-based techniques are of little use in the routine diagnosis of malaria because, in most settings, operational issues result in an unacceptable delay in providing results. Polymerase chain reaction (PCR) may have a role as the second-line test of choice for difficult cases and situations in which low parasitemia infection is suspected (eg, suppression with antimalarial chemoprophylaxis, *P malariae* infection).⁴⁵ Attempts to develop a simple PCR-based assay for use in endemic areas are continuing.⁴⁶

MANAGEMENT

The management of malaria depends on the species involved. If there is doubt or difficulty identifying the infecting species, management should be as for *P falciparum* infection while clarification as to the infecting organism is sought (a separate thick

and thin blood slide should be sent to the local reference laboratory, ideally accompanied by ethylenediamine tetraacetic acid (EDTA) blood in case PCR is required). In all cases, management should be undertaken in conjunction with a physician experienced in dealing with malaria.

Drug therapy for malaria has been transformed by the introduction of artemisinin-containing combination therapies (ACTs). Although their mechanism of action remains uncertain, artemisinins act on almost all stages of the *Plasmodium* erythrocytic cycle, causing rapid falls in parasitemia. In addition, by killing the early ring forms, artemisinin derivatives are able to prevent the development of the more mature trophozoites and schizonts that sequester and cause severe disease.⁴⁷ Globally, the main challenges in the treatment of malaria are delivering these lifesaving drugs to the poor and vulnerable at greatest risk and ensuring that resistance is contained.⁴⁸

Falciparum Malaria

P falciparum infection is categorized as severe or nonsevere (also known as complicated and uncomplicated) malaria. This categorization is based on the presence of at least 1 of the WHO severe malaria criteria (see **Box 1**). These criteria were developed and validated in studies largely of African children and Asian adults with positive slides for *P falciparum*. However, there have subsequently been several studies that have described the use of these criteria in the context of managing malaria in patients returning to a resource-rich setting from a visit to an endemic setting (imported malaria).^{27,37,38,49–55}

Nonsevere Falciparum Malaria

Drug treatment

Recommendations on the treatment of nonsevere malaria vary from country to country. Both CDC and UK guidelines suggest that treatment should not be started until there has been a laboratory-confirmed diagnosis, except in exceptional circumstances.^{44,56} Treatment should be started urgently once falciparum malaria has been diagnosed, with priority given to starting some form of treatment rather than the precise choice of treatment. A preferred, but not immediately available, treatment can always be substituted after a less ideal, but available, treatment has been begun.

The WHO recommends that ACTs are the first-line treatments for uncomplicated falciparum malaria. Five ACTs are recommended by the WHO (**Table 2**), the choice depending on local availability and, in some cases, resistance to the nonartemisinin component.³⁴ The CDC still recommends chloroquine for disease acquired in regions where falciparum is chloroquine sensitive. For disease acquired in areas of known chloroquine resistance or where resistance is unknown, CDC suggest a choice of atovaquone-proguanil (Malarone), artemether-lumefantrine (Coartem), or quinine plus doxycycline/tetracycline/clindamycin, with mefloquine only when the other options cannot be used.⁵⁶ UK guidelines recommend that chloroquine should no longer be used for the management of falciparum malaria and are similar to the CDC guidelines for the management of malaria from chloroquine-resistant areas.⁴⁴ Treatments for nonsevere falciparum malaria recommended by CDC and UK guidelines are shown in **Table 3**.

Admission to hospital of imported nonsevere falciparum malaria

CDC and UK guidelines suggest that all patients with falciparum malaria should be admitted to monitor response to treatment and observe for progression of disease severity.^{44,56} The basis of these recommendations is the significant mortality among young, previously fit patients and the observation that patients can rapidly deteriorate despite initially presenting with less severe disease.⁵⁷ There has been increasing interest in the question of whether a subgroup of patients can be treated as outpatients

Drug	Area Malaria Acquired			Comments
	Africa	East Asia	Other	
Artemether/lumefantrine	+	+	+	Should be taken after a meal containing fat to aid absorption
Artesunate/amodiaquine	+/-	-	+	Resistance to amodiaquine component reported, limiting use in East Africa
Artesunate/mefloquine	+	+	+	Increased dysphoria, sleep disturbance, nausea, and vomiting reported in trials Widely used in southeast Asia for resistant <i>P falciparum</i>
Artesunate/sulfadoxine-pyrimethamine	+/-	-	+	Resistance to sulfadoxine-pyrimethamine component reported, limiting use in East Africa
Dihydroartemisinin/piperaquine	+	+	+	Widely used in southeast Asia for resistant <i>P falciparum</i>

for nonsevere falciparum malaria. Several case series have been cited in defense of this policy.^{50,51,55,58} Together, these series describe 400 adults treated as outpatients and claim to show no adverse outcomes, although a small proportion (13/400, 3.25%) of patients required admission after therapy had been started. These series were in

Drug	Dose (60 kg Adult)	Comments
Artemether-lumefantrine	4 tablets at 0, 8, 24, 36, 48, and 60 h	WHO first-line treatment in adults, children, and pregnancy after the first trimester Should be taken after fatty meal
Atovaquone-proguanil (Malarone)	4 tablets once a day for 3 d	May cause diarrhea and vomiting
Quinine	600 mg every 8 h for 5–7 d With Doxycycline 200 mg once a day for 7 d Or Clindamycin 450 mg 3 times a day for 7 d	Often causes reversible tinnitus and deafness. Itch in dark-skinned patients Not in children or pregnancy. May cause gastritis Choice in pregnancy and children <12 y
Chloroquine	600 mg base followed by 300 mg at 6, 24, 48 h	Not in UK guidelines Only if acquired in chloroquine-sensitive region (CDC guideline)
Hydroxychloroquine	620 mg base followed by 310 mg at 6, 24, 48 h	Not in UK guidelines Only if acquired in chloroquine-sensitive region (CDC guideline)

a variety of settings, although all are likely to have occurred where there was significant expertise in slide reading and the management of malaria. Consequently these studies may not be representative of many of the settings where infection is being treated. None of these studies involved the use of ACTs, which should result in faster parasite clearance and are better tolerated than older drugs such as quinine.^{59,60} Given these difficulties in interpreting the current data, we think that outpatient management of falciparum malaria should only be considered in selected individuals in centers with experience of managing the disease, ideally as part of prospective studies or randomized trials.

Severe Falciparum Malaria

Drug treatment

Two large-scale trials in southeast Asia and Africa have shown the superiority of artesunate compared with quinine for the treatment of severe malaria.^{35,36} A recent Cochrane review showed a 39% (95% confidence interval [CI] 25%–50%) reduction in the risk of death when an adult with severe malaria was treated with artesunate rather than quinine, with a 24% (95% CI 10%–35%) reduction in children.⁶¹ Although these studies have made it imperative to deploy artesunate as the first-line antimalarial for severe malaria in endemic regions, some remain concerned about the use of artesunate for the treatment of severe imported malaria.⁶² These concerns focus on the unblinded nature of the trials, the extrapolation of results from endemic countries to nonendemic countries, and the lack of an approved product. In addition, recent studies have shown previously unforeseen adverse effects, with neutropenia occurring in both African children coinfecting with human immunodeficiency virus (HIV) and receiving oral artesunate-amodiaquine⁶³ and in Cambodian adults treated with high doses of artesunate monotherapy.⁶⁴ A retrospective analysis of travelers treated for severe malaria with intravenous artesunate has highlighted severe and unexplained late hemolysis occurring up to 3.5 weeks after cessation of artesunate.⁶⁵ Despite these concerns the data clearly indicate the superiority of artesunate for the treatment of severe malaria, there is therefore a need for a robust reporting system to record potential adverse events as artesunate is more extensively prescribed. An approved preparation of intravenous artesunate is likely to be available by the end of 2012.

As a result of the concerns described earlier, although largely resulting from the lack of a fully approved formulation of artesunate, many guidelines outside endemic areas do not endorse artesunate as the first-line antimalarial for severe disease. Notable approaches to this predicament have been made in Australia, where supplies of artesunate are sourced from Guilin Pharmaceuticals in China, batch tested for purity, stability, and sterility, and distributed to hospitals across the country and in the United States, where the CDC have arranged to provide artesunate sourced from the Walter Reed Army Institute of Research as an investigational drug.

Drugs recommended by CDC and UK guidelines for the treatment of severe falciparum malaria are shown in **Table 4**. Of critical importance in managing severe malaria is to urgently administer one of these treatments. It is important to follow quinine or artesunate therapy with a second antimalarial, once the patient is able to tolerate oral medications, to clear residual parasitemia and prevent recrudescence.

Supportive care

Severe malaria is a life-threatening condition and should be managed in an appropriate setting. Supportive care is similar to that for other severe infections, although direct evidence for goal-directed therapy in severe malaria as recommended for severe sepsis⁶⁶ is lacking and there is some uncertainty about the fluid management of severe malaria. One large randomized controlled trial of fluid bolus in African

Drug	Dose (Adult)	Comments
Artesunate	2.4 mg/kg IV at time 0, 12, 24, and every 24 h Until able to take oral medication (minimum 3 doses)	Avoid in first trimester Unlicensed drug, in the United States, contact CDC for supply Follow-on therapy with a full course of any appropriate drug from Table 3
Quinidine gluconate	6.25 mg base/kg (=10 mg salt/kg) loading dose IV over 1–2 h, then 0.0125 mg base/kg/min (=0.02 mg salt/kg/min) continuous infusion for at least 24 h or 15 mg base/kg (=24 mg salt/kg) loading dose IV infused over 4 h, followed by 7.5 mg base/kg (=12 mg salt/kg) infused over 4 hours every 8 hours, starting 8 h after the loading dose Until parasite density <1% and patient can take oral medication, complete treatment with oral quinine, dose as nonsevere malaria	Not in United Kingdom Risk of arrhythmia and hypotension Risk of hypoglycemia Quinidine/quinine course = 7 d in southeast Asia and 3 d in Africa or South America Follow-on or overlapping therapy with a full course of any appropriate drug from Table 3
Quinine dihydrochloride	20 mg/kg loading dose IV over 4 h followed by 10 mg/kg IV infusion every 8 h Dosing interval should be reduced to 12 hourly if IV therapy continuing for more than 48 h Until patient can tolerate oral therapy Minimum of 5 d quinine (given IV or oral) recommended (unless Coartem used as follow-on)	Avoid loading dose if quinine or mefloquine administered within 12hrs Risk of arrhythmia and hypotension Risk of hypoglycemia Reversible tinnitus and deafness common. Itch in dark-skinned patients Choice in first trimester Follow-on or overlapping therapy with a full course of any appropriate drug from Table 3

Abbreviation: IV, intravenous.

children with severe infection and signs of poor perfusion found a significant increase in mortality associated with fluid bolus therapy.⁶⁷ Around 60% of these children had infection with *P falciparum*, and results in this subgroup were similar to those without malaria. Although it would be a mistake to extrapolate such results to other settings where better resources allow for more intensive monitoring and intervention, proposed UK guidelines in children may need review in the light of this evidence.⁶⁸ UK guidelines for management of adults with severe malaria suggest monitoring of central venous pressure with the aim of maintaining perfusion with a right atrial pressure less than 10 cm H₂O, whereas WHO guidelines suggest a central venous pressure of 0 to 5 cm H₂O as a target, in the belief that this may help to avoid ARDS.^{34,44} However,

recent data are challenging the usefulness of such targets and questioning whether they achieve improvements in microvascular flow, although it is still advised that overzealous fluid resuscitation should be avoided.^{69,70}

Although bacterial coinfection in severe imported malaria is thought to be uncommon, a European case series identified community-acquired infection in 30/400 (7.5%) admissions to an intensive care unit with severe malaria, including 10 cases of bacteremia and 13 cases of pneumonia.³⁸ Blood culture should be performed in all patients presenting with severe malaria and there should be a low threshold for broad-spectrum antibiotics. Further data describing the prevalence of community-acquired bacteremia associated with imported malaria are needed.

Both quinine and quinidine can induce hyperinsulinemic hypoglycemia, a complication significantly less common with artesunate therapy.^{35,36,61} Close blood glucose monitoring should be in place for all patients with severe malaria. Quinine and quinidine can both cause lethal hypotension if given rapidly because of their α -blocking activity, necessitating administration by controlled infusion. Both quinine and quinidine prolong the QRS complex and the QT interval, although the effect on the QT interval is about 4 times as severe for quinidine.⁷¹ All patients receiving parenteral quinidine should have continuous cardiac monitoring.⁵⁶ Older patients and those with preexisting cardiac disease receiving parenteral quinine therapy should have continuous cardiac monitoring.⁴⁴

Adjunctive treatments

Many adjunctive therapies to reduce mortality in malaria have been trialed, including dexamethasone, anti-tumor necrosis factor- α antibodies, pentoxifylline, deferoxamine, *N*-acetylcysteine, heparin, aspirin, and mannitol.⁷² There is no evidence that any of these therapies is effective in reducing mortality.

Intravenous artesunate therapy, with its rapid reduction in circulating parasitemia, may render exchange blood transfusion (EBT) or erythrocytapheresis unnecessary.⁴⁴ CDC guidelines currently recommend EBT be considered if parasitemia is greater than 10%, or cerebral malaria, ARDS, or renal complications exist.⁵⁶ UK guidelines are more stringent, suggesting EBT if parasitemia is greater than 30% or greater than 10% with other manifestations of severe disease.⁴⁴ Robust evidence supporting the use of EBT is lacking,⁷³ although there have been numerous case reports and case series of its effective use.

Non-Falciparum Malaria

The management of vivax and ovale malaria is divided into management of the acute fever, and management of hypnozoites to prevent relapses. *P. malariae* and *P. knowlesi* have no hypnozoite stage, and treatment targeted at the acute illness is sufficient.

If there is doubt as to the infecting species, treatment of the acute illness should be as for falciparum malaria (see **Table 3**); following expert review of the blood film, treatment of hypnozoites can be administered at a later date if necessary.

The recommended treatment of acute non-falciparum malaria is chloroquine, usually given as 600 mg base initially, followed by 300 mg 6 to 8 hours later and 300 mg on days 2 and 3.^{44,56} With severe disease and a lack of injectable chloroquine, quinine, quinidine, or artesunate can be used at doses as for severe falciparum malaria.

The only drugs currently licensed for the prevention of relapse are based on the 8-aminoquinoline primaquine. Both primaquine and a related compound, tafenoquine, can cause severe hemolysis in patients with glucose-6 phosphate dehydrogenase (G6PD) deficiency and patients should be tested for this deficiency before primaquine therapy. The genetics of G6PD deficiency are complex and primaquine-related hemolysis is variable within this condition. If hemolysis is likely to be clinically significant,

there are several possible approaches to treatment to prevent relapse. First, chloroquine can be prescribed at a weekly prophylactic dose for 6 months to cover the period of highest risk of relapse, or, second, a treatment course of chloroquine can be issued with the advice to start therapy if a fever is detected. Third, a prophylactic course could be provided for use during periods in which a clinical episode of malaria would be most disadvantageous.

Personal Prevention and Chemoprophylaxis

A combination of measures is necessary to prevent malaria and reduce morbidity in travelers. These measures include awareness of malaria risk, the use of bite-avoidance measures, using chemoprophylaxis, and seeking an early diagnosis, which is remembered through the mnemonic ABCD.

The malaria risk to travelers is usually defined by national or international guidelines, and preventative policy is based on a combination of rate of infection or transmission intensity of malaria, species of malaria, and geographic distribution, including altitude and seasonality. The risk of acquisition of an infection has, until recently, been a consensus opinion of policy makers based on local population malaria. More recently, the incidence in travelers has allowed more precise estimates to be defined; for the average traveler to Vietnam, Thailand, Cambodia, and China, the risk of all malaria is less than or equal to 1 case per 100,000 visits, and, for all travelers to West Africa, the risk is 169 and for East Africa (Kenya) 7 per 100,000 visits.^{74,75} The risk depends on the reason for travel, and individuals who visit friends and relatives (VFR) have a 3-times higher malaria incidence than travelers visiting for other reasons.⁷⁴ The reliance on prescribing chemoprophylaxis for the prevention of malaria is based on the unreliable use of personal bite prevention measures related to incorrect health beliefs and low adherence to advice. Most VFR travelers who develop malaria have not sought advice or used malaria chemoprophylaxis during their travel.

Malaria chemoprophylaxis is the use of antimalarial medication to prevent the symptoms of malaria. Regimens may act as causal prophylactics, in which the drug acts on the parasite in the liver tissue, for example atovaquone-proguanil and primaquine, or as suppressive prophylactics acting on blood-destroying erythrocytic parasites; these include mefloquine, proguanil, chloroquine, and doxycycline, or both.

For regions in which chloroquine-resistant *P. falciparum* is the predominant species, the regimens recommended by most policy groups are either atovaquone-proguanil (Malarone) doxycycline, or mefloquine. The choice of regimen depends on several variables, which include adverse event profile, and, in particular, the reputation of the regimen held by the traveler, duration of travel, and prior medical problems. Cost and simplicity of a regimen have a bearing on final choice, as does the health advisor's preference of drug. Efficacy as a schizonticidal agent is similar for the 3 regimens, but effectiveness as a combination of efficacy and adherence may be different. The mild to moderate adverse event profiles of the 3 regimens are similar, with 45% of chloroquine and proguanil users, 42% of mefloquine users, 33% of doxycycline users, and 32% of atovaquone/proguanil users reporting mild to moderate problems. Significant adverse events (that interfered with daily activity) were reported in 11% of mefloquine users, 12% of chloroquine plus proguanil users, 6% of doxycycline users, and 7% of atovaquone and proguanil users. Neuropsychiatric events were reported in as many as 42% of mefloquine users and 30% of atovaquone and proguanil users, respectively, during blinded use of chemoprophylaxis.^{76,77} Incidence of serious adverse events requiring hospitalization are not well understood but are important where the risk of malaria is low, and may be an important cause of morbidity when used in settings with low malaria prevalence.

Bite Prevention

The 2 major strategies used to prevent bites are the application of topical repellents and barrier methods to reduce contact with biting arthropods. Deet (diethyltoluamide) is the best broad-spectrum repellent available with an extensive safety history and is a compound with which newer repellents are compared in reducing nuisance bites from arthropods. Icaridin (2-(2-hydroxyethyl)-piperidinecarboxylic acid 1-methyl ester) and PMD (p-methane 3,8-diol) are reasonable alternatives to Deet for those visiting areas where arthropod-borne diseases are endemic. IR3535 (ethyl butylacetylaminopropionate) has lower efficacy against anopheles mosquitoes and should not be advised for areas where malaria is endemic. The higher concentrations of active repellent results in longer duration of activity but Deet concentrations of more than 50% have little added benefit.

The use and benefit of insecticide-treated mosquito nets is clear and should be advised for all travelers visiting endemic areas where there is a risk from biting arthropods when asleep. The usefulness of electric insecticide vaporizers, essential oil candles, and burning cardboard to reduce bites from arthropods has some benefits but the benefit of knockdown insecticide sprays is minimal.⁷⁸

EARLY DIAGNOSIS

Many malaria deaths in travelers result from a delay in diagnosis of malaria. The reasons for the delay are multifactorial. Education on preventing delay in seeking medical help for malaria must be provided at the pretravel consultation. Preventing delays in recognizing and testing for malaria at the first medical contact requires educating physicians and other health professionals on appreciating the symptoms and signs of malaria.

MALARIA AND PREGNANCY

In highly endemic areas where immunity to severe disease is acquired in childhood, malaria may account for up to one-half of all low birth weight babies and one-quarter of severe maternal anemia.⁷⁹ In this context, severe disease is confined largely to primigravidas, and pregnant women coinfecting with HIV. Malaria in the multigravida pregnancy can present insidiously with little sign of the infection other than anemia and fetal growth retardation. In contrast, all pregnant women from nonendemic settings are at increased risk of severe malaria and potentially severe consequences for them and their pregnancy. Consequently a low threshold for admission should be applied to pregnant women returning with fever from regions where malaria is endemic, and pregnancy itself is considered by many as a criteria for intravenous therapy if falciparum malaria is diagnosed. Obstetric advice should be sought early in such cases and patients should be monitored closely for hypoglycemia, which is common in this context. Artesunate and artemisinin combination therapies should be avoided if possible in the first trimester of pregnancy. Women who are pregnant when traveling to areas where malaria is endemic should be advised of the increased disease severity and encouraged not to travel. Mefloquine chemoprophylaxis has been used in pregnant travelers and no unexpected outcomes to pregnancy have been reported when used during pregnancy.

SUMMARY

Despite efforts to control malaria, it continues to claim the lives of more than 2000 people every day and remains the most important human parasitic disease. The

development of artemisinin combination therapies for nonsevere malaria and parenteral artesunate for severe malaria represent the most important advances in antimalarial therapeutics. Progress in reducing global mortality depends on ensuring that such treatments reach those most in need. These drugs also offer the clearest therapeutic advance in managing imported malaria, although the greatest benefits available are in prevention, early recognition, and early treatment.

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