Malaria

Naomi F Walker
Behzad Nadjm
Christopher J M Whitty

Abstract

Malaria remains a leading cause of mortality worldwide and a cause of morbidity in returning travellers in the UK. The management of malaria, recent advances in diagnosis and current areas of controversy are summarized, primarily for clinicians in non-endemic countries who do not routinely encounter it. The most important message is that malaria is very common and presentation is non-specific, so a malaria test is essential. Early diagnosis and prompt effective treatment prevent unnecessary deaths. Health promotion for travellers to endemic areas is essential to reduce the burden of imported malaria.

Keywords *Anopheles*; antimalarials; falciparum; knowlesi; malaria; malariae; ovale; *Plasmodium*; vivax

What's new?

- Rapid diagnostic tests are increasingly used in clinical practice as an adjunct to (not a replacement for) microscopy
- Elderly patients are at particular risk of mortality
- Clear evidence suggests intravenous artesunate is preferable to intravenous quinine for severe malaria and is increasingly used in clinical settings, despite supply difficulties
- Reports of artesunate-resistant falciparum malaria and chloroquine-resistant vivax malaria exist, although they do not affect first-line therapy in most settings

Introduction and epidemiology

In the last decade, investment in malaria control strategies has contributed to a significant reduction in malaria cases and deaths worldwide. Despite this, malaria remains a leading cause of morbidity and mortality, with an estimated 219 million cases and 660,000 deaths in 2010. The burden of disease lies in Africa and is associated with poverty. Of all malaria deaths, 86% occur in children under 5 years.[1] In parts of Africa, the average person will catch malaria four or more times a year, so the disease is much more common than influenza in the UK. In addition, whereas global access to malaria diagnostics and effective treatments is improving, emerging anti-malarial drug resistance is a cause for concern.[2]

In Europe and the USA, malaria is an important imported infection and is likely to be increasingly so as tourism and other travel to malaria-affected regions steadily increase. Malaria is the leading potentially fatal cause of febrile illness in returned travellers.[3] Although uncomplicated malaria is rarely fatal, European case fatality rates for falciparum malaria are around 1%, and up to 25% in an intensive care setting.[4,5] Factors associated with the development of severe malaria include older age, increased time to presentation and delayed diagnosis, pregnancy and HIV infection. Most patients returning to Europe with malaria do not report taking malaria prophylaxis.[6]

This article, aimed at clinicians in non-endemic countries, addresses clinical aspects of malaria pathophysiology, presentation, diagnosis and management, highlighting recent developments and areas of controversy. Every death from malaria should be preventable if the condition is diagnosed early and treated promptly with effective drugs. The most important messages from this article are that malaria is common and that imported malaria can be largely prevented by effective prophylaxis.[4]

Pathophysiology

Malaria is caused by protozoal parasites of the genus *Plasmodium*. Five species of *Plasmodium* cause disease in humans (Table 1); falciparum malaria causes almost all the deaths. In humans, malaria is transmitted by female *Anopheles* mosquitoes that bite typically after dark.

The pathophysiology of disease is incompletely understood. The virulence of *Plasmodium falciparum* is related to the blood stage of the parasite and is multifactorial including:

- sequestration (sticking down) of infected red blood cells within the microcirculation, probably causing hypoxia of tissues, especially the brain
- infection of erythrocytes of all ages, compared to other forms of malaria that are selective for younger cells, enabling higher levels of parasitaemia
- activation of various parts of the immune system, leading to cytokine-driven pathology.[7,8]

Plasmodium vivax and *Plasmodium ovale* malaria lay down hypnozoites in the liver. The parasite lies dormant in these cells for months or even years, emerging to cause clinically apparent malaria, often several times. Consequently, infection with these species requires separate treatment directed at eliminating the hypnozoite stage.

Naomi F Walker *MA MRCP DTM&H is a Wellcome Trust Clinical Research Training Fellow in Tropical Medicine and Public Health at Imperial College London, UK and University of Cape Town, South Africa. Competing interests: none declared.*

Behzad Nadjm *MRCP MD DTM&H is a Senior Clinical Researcher at the Oxford Clinical Research Unit, Hanoi, Vietnam, and Honorary Consultant Physician at University College London Hospitals NHS Trust, UK. Competing interests: none declared.*

Christopher J M Whitty *FRCP is a Consultant Physician at the Hospital for Tropical Diseases and University College London Hospitals NHS Trust, and Professor of International Health at the London School of Hygiene & Tropical Medicine, UK. Competing interests: none declared.*

Species of *Plasmodium* causing human disease

Species	Distribution	Severe disease	Recurrent disease (relapses)	Features
P. falciparum	Widespread	+++	−	Most fatalities Severe disease
P. vivax	Widespread	+	+	Hypnozoites present: long incubation
P. ovale	West Africa	(+)	+	and relapse possible
P. malariae	Africa	(+)	−	Long incubation possible Cause of nephrotic syndrome
P. knowlesi	Malaysia, Thailand, Myanmar	+	−	Zoonosis Microscopically similar to *P. malariae* Severe disease/fatalities

(+) Very rare.
+ Rare.
+++ Common.
See: Cox-Singh J, Davis TME, Lee K, et al. Plasmodium knowlesi malaria in humans is widely distributed and potentially life-threatening. *Clin Infect Dis* 2008; **46:** 165–71.

Table 1

Clinical manifestations of disease

Symptoms develop from around 6 days after an infected bite. Most falciparum infections present within 1 month, but can do so later, especially in those taking prophylaxis. Vivax, malariae and ovale infections commonly have a longer incubation period and vivax and ovale can relapse after an extended period because of activation of hepatic hypnozoites. This is different from recrudescence where parasites reappear in the blood following failed treatment that has not completely cleared parasites. *P. vivax*, *P. ovale* and *Plasmodium malariae* are much less likely to cause severe disease than *P. falciparum* but falciparum and malariae malaria do not relapse. A second episode of falciparum malaria suggests treatment failure or re-infection.

A history of fever is usual, although not invariable; because the temperature fluctuates it may not be found at presentation.[9] Other symptoms are non-specific and can be misleading, commonly resulting in misdiagnosis such as influenza, hepatitis, gastroenteritis or meningitis. If a patient is unwell and has recently returned from malarial areas the only way to exclude malaria is to do an urgent malaria test.

If malaria is diagnosed (or suspected), assessing for features of severe malaria, which differ between children and adults[10] (Table 2) is crucial. The presence of any of these features constitutes potentially severe malaria. In children with severe falciparum malaria, respiratory distress, anaemia, convulsions and hypoglycaemia are more common than in adults. Pulmonary oedema, acute respiratory distress syndrome (ARDS) and acute renal failure occur rarely in children, but occur in over half of all cases of life-threatening malaria in non-immune adults.

Diagnosis

Diagnostic delay, either because the patient presents late, or because a doctor has not suspected the diagnosis, is a key factor in mortality from malaria in non-endemic countries.[11] Suspecting the diagnosis is paramount and malaria can occur even with perfect prophylaxis. If malaria tests are negative and the patient appears well, they should return for a repeat test the next day; occasionally the first test can be negative. More than three tests are unnecessary to exclude malaria in a single febrile episode unless symptoms change. It is important to consider that travellers returning from malaria-endemic regions who test negative

Features of severe or potentially complicated malaria

	Adult	Child
Clinical		
Confusion, drowsiness or coma	+++	+++
Generalized convulsions	+++	++++
Acute pulmonary oedema/ARDS/ALI	++	+
Respiratory distress (acidosis)	+	+++
Jaundice (haemolytic)	++	+
Shock – 'algid malaria'	++	++
Abnormal bleeding (generally DIC)	+	+
Very dark urine – 'blackwater fever'	(+)	+
Prostration (extreme weakness without other signs)	+	+++
Laboratory findings		
Hyperparasitaemia (>5%)[a]	+++	+++
Acute renal failure	+++	+
Severe anaemia (Hb <8.0 g/dl)	++	+++
Hypoglycaemia[b]	++	+++

+ Rare, ++ Uncommon, +++ Common, ++++Very common.
ALI, acute lung injury; ARDS, adult respiratory distress syndrome; DIC, disseminated intravascular coagulation.
Adapted from Guidelines for the treatment of malaria. World Health Organization; 2nd edn, 2010.
[a] UK guidelines suggest >2% as an indication for parenteral therapy (UK Malaria Treatment Guidelines. Lalloo DG, Shingadia D, Pasvol G, Chiodini PL, Whitty CJ, Beeching NJ, Hill DR, Warrell DA, Bannister BA. *J Infect* 2007; **54**(2): 111–121).
[b] Common in pregnant women.

Table 2