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REVIEW ARTICLES

Managing malaria in the intensive care unit

M. Marks[1,2], A. Gupta-Wright[1,2], J. F. Doherty[1], M. Singer[3] and D. Walker[3]*

[1] The Hospital for Tropical Diseases, Mortimer Market Centre, Capper Street, London, UK
[2] Department of Clinical Research, Faculty of Infectious and Tropical Diseases London School of Hygiene and Tropical Medicine, Keppel Street, London, UK
[3] Department of Critical Care, University College London Hospital NHS Foundation Trust, 3rd Floor, 235 Euston Road, London NW1 2BU, UK
* Corresponding author. E-mail: david.walker@uclh.nhs.uk

Editor's key points

- The authors describe the presentation and management of malaria on the ICU.
- They review the literature and provide management strategies for dealing with this life-threatening condition.

The number of people travelling to malaria-endemic countries continues to increase, and malaria remains the commonest cause of serious imported infection in non-endemic areas. Severe malaria, mostly caused by *Plasmodium falciparum*, often requires intensive care unit (ICU) admission and can be complicated by cerebral malaria, respiratory distress, acute kidney injury, bleeding complications, and co-infection. The mortality from imported malaria remains significant. This article reviews the manifestations, complications and principles of management of severe malaria as relevant to critical care clinicians, incorporating recent studies of anti-malarial and adjunctive treatment. Effective management of severe malaria includes prompt diagnosis and early institution of effective anti-malarial therapy, recognition of complications, and appropriate supportive management in an ICU. All cases should be discussed with a specialist unit and transfer of the patient considered.

Keywords: ARDS; ICU; imported infections; malaria

The number of people who travel to malaria-endemic areas continues to increase (Fig. 1).[1] Malaria is responsible for the death of at least three quarters of a million people worldwide every year[2] and is the commonest cause of serious imported infection in non-endemic areas.[3–5] Severe malaria is mostly caused by *Plasmodium falciparum*, although other species can cause severe disease.[6 7]

Recommendations for the management of severe imported malaria are largely derived from trials in endemic regions and retrospective series of imported malaria. In spite of advances in management, the mortality rate of severe malaria remains ~10% and data from the UK suggest that the outcome may be worse for patients managed in centres with less experience of treating the disease.[8] This review is based on recent studies of anti-malarial and supportive therapies and outlines the epidemiology of malaria, clinical manifestations, and risk stratification of severe disease, and provides an update on the management of patients with imported malaria requiring intensive care unit (ICU) support.

Epidemiology

Malaria is endemic throughout most of the tropics and subtropics and is one of the commonest causes of febrile illness in returning travellers.[3–5] There were 6749 cases of imported malaria reported within the European Union in 2010 (0.99 cases per 100 000)[9] and 1688 cases reported in the USA (0.55 cases per 100 000).[3] In Europe, four countries (France, UK, Germany, and Italy) account for 80% of all cases. Surveillance from both Europe and the USA show that most cases of falciparum malaria are acquired in sub-Saharan Africa.[3 10–12] Compared with malaria in endemic settings, where children are most commonly affected, imported malaria is predominantly a disease of young- and middle-aged adults—the median age of cases in the UK is 31 years.[13]

Surveillance data demonstrate that individuals originating from endemic regions who travel to 'visit friends and relatives' are more likely to develop malaria than people who travel for other reasons (relative risk 3.65),[5 13] although these individuals may be at reduced risk of developing severe disease because of partial immunity.[11 14] Anti-malarial chemoprophylaxis is very effective but surveillance data consistently demonstrate that most travellers do not take it appropriately.[3 13 15] Reasons for poor adherence include an assumption of low risk, particularly among individuals who grew up in endemic regions, and concerns about potential drug side effects.

Nearly all severe disease is caused by falciparum malaria; ~10% of patients with imported falciparum malaria are reported to develop severe disease.[3 16] The case fatality rate is ~1%.[3 13] UK surveillance data demonstrate significantly higher mortality (odds ratio 10.68) in patients aged >65 yr compared with adults aged 18–35 yr and among tourists compared with patients originally from endemic countries (odds ratio 8.2).[8] Death from non-falciparum malaria is extremely rare with a case fatality rate of 0.05%.[8]

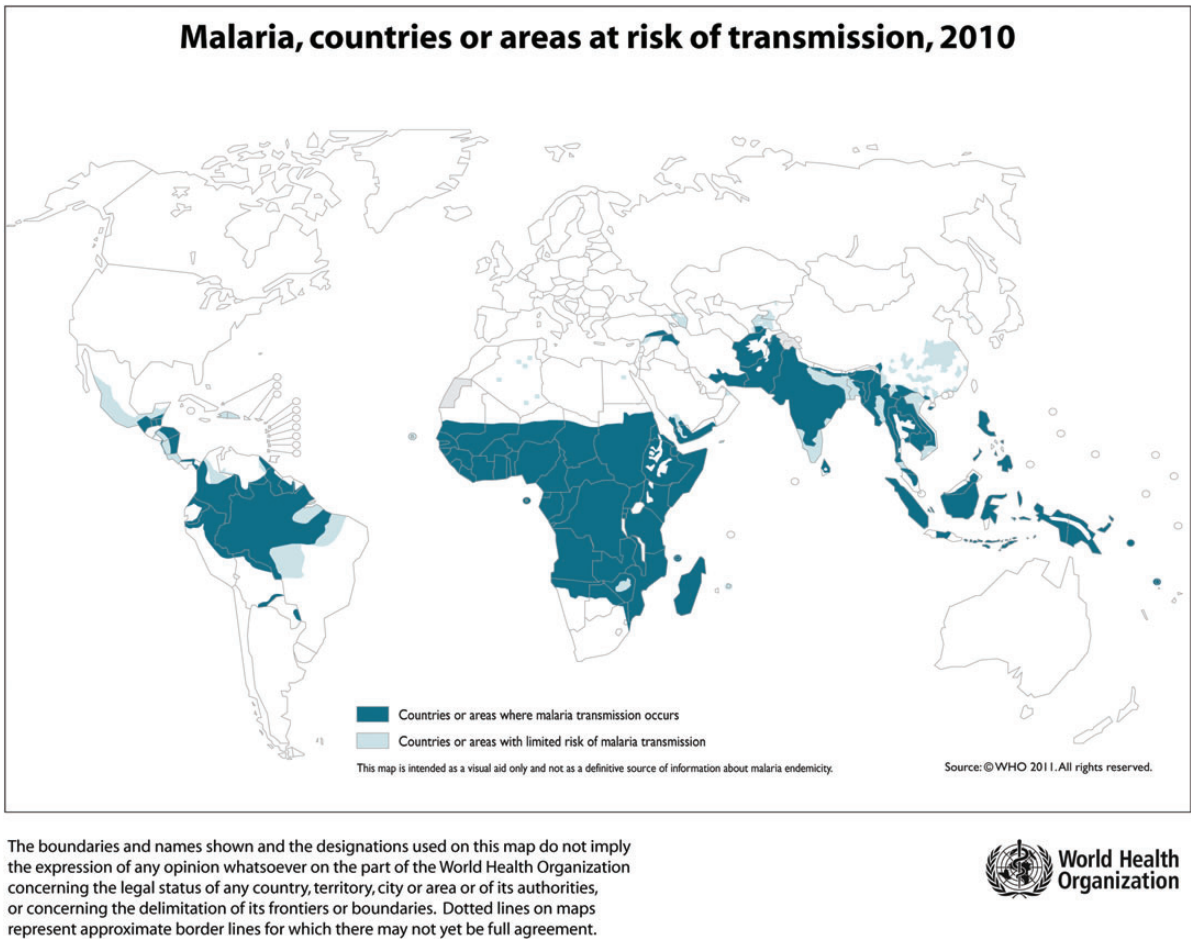

Fig 1 Countries and areas with risk of malaria transmission. Map from WHO International Travel and Health Programme, http://www.who.int/ith/en/. Reproduced with permission of the World Health Organisation.

Pathophysiology

Malaria is caused by infection with the protozoan parasite *Plasmodium* and is transmitted by female Anopheline mosquitoes.[17] Four species are classically considered to cause disease in humans (*P. falciparum*, *Plasmodium vivax*, *P. ovale*, and *P. malariae*) although a fifth, *P. knowlesi*, is now recognized as a zoonotic cause of malaria in parts of Malaysia.[18] After the bite of an infected Anopheline mosquito (Fig. 2), the inoculated sporozoites are taken up by hepatocytes where they mature over 7–10 days to form schizonts. These then rupture to release variable numbers of merozoites into the blood. Merozoites rapidly invade erythrocytes, forming trophozoites, which again mature into schizonts over a period of 24–72 h, depending on the species. The mature schizonts then rupture causing haemolysis, releasing further merozoites into the blood where they invade more erythrocytes. With *P. falciparum*, each schizont that ruptures releases 16 merozoites into the blood. Most schizonts adhere to the lining of small blood vessels in deep tissues, a process known as sequestration. The presence of schizonts in peripheral blood implies that the parasitaemia is likely to increase significantly and is itself a marker of severe disease. Human disease is caused by these asexual stages. Gametocytes, the sexual stage, develop some days later and it is these that are taken up by mosquitoes in endemic areas, where they breed and multiply in the mid-gut, ultimately leading to sprozoites found in the mosquitoes' salivary glands. Gametocytes are frequently seen on blood films but, by themselves, are of no clinical significance.[19]

The incubation period for falciparum malaria is usually 12–14 days and slightly longer for non-falciparum species. One series of imported malaria reported a median of 9.5 days (IQR 3–14) between return from a malaria-endemic area and hospital admission.[11] Progression to severe disease is variable; however, the largest series of severe imported malaria found a mean duration of symptoms of 5.5 days before ICU admission.[20]

Infection with *P. falciparum* results in the expression of *P. falciparum* erythrocyte membrane protein 1 (*Pf*emp1), an important virulence factor, on the surface of red blood cells. *Pf*emp1 mediates binding of infected red blood cells to endothelial surfaces and sequestration in capillary beds.[21] *Pf*emp1 is encoded by the *var* family of genes and the parasite regularly switches between ~60 variants of this gene resulting in