Treating malaria in the UK

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Abstract

Imported malaria remains a significant cause of mortality and morbidity in children travelling to areas of the world endemic for malaria. Malaria is one of the commonest imported tropical diseases in the UK, with infection acquired most commonly in sub-Saharan Africa. Over 80% of all cases of malaria are due to *Plasmodium falciparum*, which can cause severe or life-threatening multi-organ disease in children. The clinical features of malaria in children are protean and often non-specific resulting in missed or delayed diagnosis. Children are more likely than adults to deteriorate rapidly and to develop severe malaria, particularly cerebral malaria. Malaria should be suspected in all children with a history of travel to a malaria endemic country who present with fever. Diagnosis is usually made with repeated thick and thin blood films. Delays in diagnosis are associated with an increased risk of developing severe malaria and death. Appropriate anti-malarial therapy and supportive care should be instituted as soon as possible, particularly in children with severe malaria. Advice should be sought early from an appropriate specialist.

Keywords child; imported; malaria; treatment

Background

Malaria is a vector-borne infection in humans caused by *Plasmodium* parasites that are transmitted by female *Anopheles* mosquitoes. The main species known to infect humans are *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae.* Human infection with *Plasmodium knowlesi*, an infection typically of primates in Southeast Asia, has increasingly been described. *P. falciparum* is typically responsible for causing the most severe disease and long-term complications, whereas *P. vivax*, *P. ovale* and *P. malariae* usually cause milder disease and are not fatal except in individuals with underlying co-morbidities. *P. knowlesi* usually causes malaria in primates and only infects humans opportunistically, but recent studies have suggested that *P. knowlesi* may contribute to a significant proportion of malaria cases in parts of Southeast Asia where such infections may be misdiagnosed as *P. malariae*. Unlike *P. malariae*, however, *P. knowlesi* has a higher rate of replication (every 24 hours), resulting in high level of parasitaemia, and may be associated with severe infection and death. Chronically infected humans are the major reservoir of malaria. Both *P. vivax* and *P. malariae* can remain dormant in the liver (so-called hypnozoite form) and emerge months to years after initial infection. Malaria may rarely be transmitted by blood transfusion or needlestick injury from infected donors. Airport malaria has also been described near international airports, presumably following a bite from an infected mosquito that has survived a long-distance air flight from an endemic country.

Malaria is one of the most common infectious diseases globally and a major cause of morbidity and mortality. In 2010, there were an estimated 219 million malaria cases worldwide and almost 660,000 deaths, mostly in the African region and in children. In Europe, the United Kingdom has one of the highest burdens of imported malaria with cases peaking in 1995 at 2500 cases followed by a gradual fall to 1677 cases in 2011. Children account for 15–20% of all cases and the estimated burden of imported malaria in the UK is 2.8/100,000 children, with *P. falciparum* accounting for over 80% of childhood cases. Over 90% of all imported malaria cases in the UK occurred among Black African children, who acquired their infection in sub-Saharan Africa while visiting friends and relatives (so-called VFR). In the world of travel medicine, VFRs have been identified as a specific group of travellers with unique attributes including being less likely to seek pre-travel advice or take antimalarial prophylaxis, having different risk factors to conventional travellers and accessing healthcare sub-optimally. VFRs may also have different exposures to infection because of their pattern of travel which may differ from the average tourist particularly travel to rural areas and for longer durations. VFRs are also more likely to delay seeking medical help when they return to their country of residence, often because of cultural, economic and language barriers.

Pathogenesis

The pathogenesis of malaria is caused primarily by the invasion of red blood cells during the erythrocytic phase of the *Plasmodium* species. In addition to red blood cell destruction and subsequent anaemia, there is also microvascular sludging and sequestration of erythrocytes in the deep vasculature resulting in interference with microcirculatory flow and subsequent tissue hypoxia. Cerebral malaria, one of the severest complications of *P falciparum* malaria, is characterized by the sequestration of parasitized red blood cells in deep cerebral vasculature with subsequent vascular occlusion and tissue anoxia which result in the development of clinical symptoms, including a diffuse encephalopathy.

Clinical presentation

The symptoms of malaria are varied and non-specific, often mimicking other common childhood illnesses and thereby sometimes called “the great masquerader”. Malaria should be considered in any child presenting with fever who has travelled to an area where malaria is endemic. Nausea and vomiting are also common clinical presentations although may also occur in other common childhood infections. Compared with adults, children are less likely to complain of chills, arthralgia/myalgia or headache but are more likely to have hepatomegaly, splenomegaly and jaundice.

Severe malaria occurs almost exclusively with *P. falciparum* infection. In the UK, 5–15% of children with imported malaria present with features of severe malaria as defined by the World Health Organization (Table 1). In imported cases, severe malaria is associated with young age (less than 5 years), delayed diagnosis and non-immunity to malaria. Children with severe malaria

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Severe or complicated malaria

Impaired consciousness or seizure
Respiratory distress or acidosis (pH < 7.3)
Hypoglycaemia (<2.2 mmol/l)
Severe anaemia (<8 g/dL)
Prostration (unable to sit or stand)
Parasitaemia >2% red blood cells parasitized

Table 1

may also develop focal neurological signs, decerebrate or decorticate posturing, spontaneous bleeding, disseminated intravascular coagulation, hypotension, cardiovascular shock, pulmonary oedema, haemoglobinuria, acute renal failure and multi-organ failure. Concurrent bacterial septicaemia is rare (less than 5%) but should be considered in children presenting with severe malaria.

Diagnosis

Diagnosis of malaria is usually made by microscopic examination of thick and thin blood films, which should be requested in any febrile child who has travelled to a malaria-endemic area in the preceding 12 months, irrespective of any chemoprophylaxis taken. If there is clinical suspicion of malaria, but initial blood films are negative (may occur in up to 7% of cases), repeat films should be examined after 12–24 hours and again after a further 24 hours. Thick blood films are more sensitive in detecting malaria parasites because the blood is more concentrated, allowing for a greater volume of blood to be examined. Thin blood smears are less sensitive but are used for identifying the *Plasmodium* species, usually based on the presence of schizonts and gametocytes that are specific in appearance for different species. Identification of species should not delay starting treatment on confirmation on thick films and it may be better to assume *P. falciparum* infection based on disease severity and travel history. Thin blood smears are also used to determine the parasite count, usually reported as percentage of red blood cells parasitized. The peripheral parasite count is often a useful measure on the extent of infection and therefore disease severity although not truly reflective of true parasite burden within all the vasculature. Recently, rapid diagnostic tests (RDT), based on detection of parasite antigens in blood, are being increasingly used to diagnose malaria. Although slightly less sensitive than good quality blood films, they are easier for the non-expert to use to detect falciparum infections. RDTs are not as specific and sensitive for detection of non-falciparum infections. Thrombocytopenia is highly suggestive of malaria in non-immune children, both in falciparum and non-falciparum malaria, and should be a prompt to repeat blood films where the initial blood films are negative.

Treatment

Uncomplicated falciparum malaria

All children suspected or diagnosed with *P. falciparum* malaria should be admitted to hospital because of the difficulty in assessing disease severity in children, the possibility of rapid progression in severity of malaria and also the potential poor tolerance of oral therapies.

Provided oral treatments can be tolerated, parenteral treatment is not needed if there are no clinical or laboratory signs of severity (Table 1). Because of a lack of evidence, guidelines vary about the threshold parasite count above which to parenteral treatment in children without symptoms or signs of severity. UK guidelines suggest parasite counts over 2%, whereas WHO suggest over 5%. Oral quinine, atovaquone–proguanil and artemether–lumefantrine can all be used for the treatment of uncomplicated malaria in children (Table 2.). The combination of oral quinine with a single dose of sulfadoxine–pyrimethamine or 7 days of clindamycin or doxycycline (for children greater than 12 years age) remains highly effective in the UK, with very low relapse rates in children. Sulfadoxine–pyrimethamine may be contra-indicated in children with G6PD deficiency or may not be easily available, in which case the alternatives of clindamycin or doxycycline should be considered. Because of bitter taste and tolerability of oral quinine, alternative oral antimalarial combinations, such as artemether–lumefantrine and atovaquone–proguanil, should be considered although there is limited experience in their use in non-endemic paediatric setting. Mefloquine is also effective but is not recommended in the UK because of its side effects and high rate of non-completion of treatment courses.

Severe malaria

The main presentations of severe malaria in children are cerebral malaria, severe anaemia and respiratory distress/acidosis. Features of cerebral malaria include depressed conscious level, seizures altered respiration and posturing (decorticate or decerebrate). Hypoglycaemia, metabolic acidosis, circulatory shock and electrolyte disturbance may also be present. Prostration (the inability to sit or stand) may also be an indicator of severe disease in children.

Severe malaria is a medical emergency, and the main priority is for patients to receive adequate doses of appropriate and effective drugs as soon as possible. Quinine or artesunate are the two drugs used for parenteral treatment of severe malaria (Table 2). Parenteral quinine has previously been recommended as first-line antimalarial therapy for children with severe falciparum malaria or non-severe malaria who are unable to tolerate oral medication. Current dosing recommendations are to give a loading dose of 20 mg/kg quinine dihydrochloride in 5% dextrose or dextrose saline as a slow infusion over 4 hours, followed by 10 mg/kg (maximum 600 mg) every 8 hours for first 48 hours or until patient can swallow. The frequency of dosing should subsequently be reduced to 12 hourly if intravenous quinine continues for more than 48 hours. Close monitoring is required for hypoglycaemia, hypoxia and seizures. Intravenous treatment should be changed to oral medication once the patient's condition improves and parasite levels fall.

Clear evidence from a large randomized trial (Artesunate versus Quinine in the treatment of severe falciparum malaria in African children or AQUAMAT) now shows that although quinine remains effective, artesunate is associated with a survival advantage (relative risk reduction of 22.5%) and a significant reduction in clinical complications (development of coma, convulsions, and deterioration of coma score). This and other clinical trials have led to a change in the WHO guidelines such that IV artesunate be used preferentially over quinine as the drug of choice in both adults and children with severe falciparum