The febrile illness of malaria: an overview of assessment, management and its prevention

Correspondence to:

Dr Bruno Gnaneswaran, University of Liverpool, Foundation Building, Brownlow Hill, Liverpool, L69 7ZX.

Telephone: +44 (0) 151 794 5927

E-mail: [B.gnaneswaran@liverpool.ac.uk](mailto:B.gnaneswaran@liverpool.ac.uk)

Co-authors:

Bruno Gnaneswaran MBBS, Meng (hons)

University of Liverpool, Liverpool, U.K.

Alder Hey Children’s Hospital, Liverpool, U.K.

Conflict of interest: none declared

Melissa Gladstone MBChB, BSc, MRCP, FRCPCH, MD, DipND

Professor in Neurodevelopmental Paediatrics and International Child Health

University of Liverpool, Liverpool, U.K.

Alder Hey Children’s Hospital, Liverpool, U.K.

E-mail: M.J.Gladstone@liverpool.ac.uk

Conflict of interest: none declared

Keywords: Malaria; Infectious disease; paediatrics; assessment and evaluation

Word count: 1884

**Abstract**

Malaria is a substantial febrile illness threat for children living in or travelling from endemic countries. It is one of the most common imported infections in the United Kingdom, and children are particularly vulnerable to deterioration if malaria is not suspected early and treated promptly. In this review we highlight the assessment of the febrile child with suspected malaria and/or severe or complicated malaria and its treatment. The aim is to treat suspected malaria as a medical emergency and to provide prompt assessment and treatment with specialist input.

**Introduction**

Malaria is a substantial febrile illness threat for children living in or travelling from endemic countries. It is one of the most common imported infections in the United Kingdom, and children are particularly vulnerable to deterioration if malaria is not suspected early and treated promptly.

**What is Malaria?**

Malaria is a protozoan infection of red blood cells. The genus responsible consists of five species of *Plasmodium*: *P falciparum, P vivax, P ovale, P malariae* and *P knowlesi*. Of these, *P falciparum* is the most prevalent species in sub-saharan Africa and is responsible for most malaria-related deaths. The majority of cases are transmitted through the bite of an infected female anopheline mosquito. Alternative and much less common routes of transmission include ‘congenital’ (transplacental), iatrogenic (e.g. via blood transfusion) and needle-stick or laboratory accident.

Worldwide, it is estimated that 228 million cases of malaria occurred in 2018, with 93% of cases occurring in Africa, 3.4% in South-East Asia and 1.2% in Eastern Mediterranean region. In that year an estimated 405,000 deaths were due to malaria globally. The most vulnerable group affected by malaria in endemic countries is children under the age of 5.

In the U.K., 1,683 cases of imported malaria were reported in 2018, of which children accounted for 11%. There were 6 deaths (all ages) from malaria per year on average in the last 10 years. The majority of cases were residents of the U.K. who had travelled abroad (Box 1).

**Assessment**

The first step in the management of malaria is to always suspect and consider the possibility of malaria as a diagnosis in a patient with a fever, who is a returning traveller or who has previously visited or lived in a malaria endemic area. Early symptoms are non-specific and do not allow a diagnosis of malaria on clinical grounds alone. Importantly, one should consider malaria, even in patients who have taken chemoprophylaxis.

The incubation period, the time elapsed between exposure to the bite of the *Anopheles* mosquito and the presentation of the first clinical sign or symptom, can vary between 9 – 30 days (Box 2).

**History**

Illness due to any species of the genus *Plasmodium*, in children with uncomplicated malaria, generally presents with fever and vomiting . Headache, chills, muscle aches and anorexia are common. Rigors can occur, especially in *P vivax* infections. Children are less likely than adults to complain of chills, arthralgia/myalgia or headaches.

Certain symptoms of malaria in children can be misinterpreted and wrongful diagnoses can be made. These include vomiting, diarrhoea and abdominal discomfort which can lead to a diagnosis of gastroenteritis; and tachypnoea, difficulty breathing and/or cough can lead to a diagnosis of pneumonia.

Prodromal symptoms of malaise, anorexia, lassitude, headache, myalgia, nausea and vomiting may precede the onset of fever for up to two days. If diagnosed and treated promptly, a child with uncomplicated malaria usually makes a full recovery.

It can be difficult to reliably distinguish severe malaria from other severe infections: impaired consciousness, seizures, respiratory distress, severe anaemia, hypoglycaemia and metabolic acidosis can be present in both severe malaria and other severe infections.

An unarousable, comatose child with confirmed *P falciparum* infection, in whom other causes of encephalopathy have been ruled out, is defined as having cerebral malaria (WHO definition. Despite recovery of consciousness in most children with cerebral malaria, ~20% die and ~10% suffer with persistent neurological sequelae.

Anaemia, due to breakdown of infected red cells and impaired bone marrow function, is a common complication of malaria in both children and adults.

**Examination**

In a child with uncomplicated malaria, fever is usual, but may be periodic, and otherwise examination is unremarkable although hepatosplenomegaly may be found and the child may be drowsy. In severe or ‘complicated’ malaria, signs suggesting one or more complications may be found, including convulsions, coma, jaundice, pallor, hyperpyrexia, bleeding and hyperventilation due to acidosis.

**Severe malaria**

The initial assessment involves an ABCDE approach.

*Airway and breathing*

Children with severe malaria may present with characteristic respiratory patterns. The two commonest respiratory patterns of severe malaria in children are: respiratory distress and depressed or irregular breathing. Respiratory distress usually takes the form of deep breathing, commonly due to acidaemia. Slow or irregular breathing may be a sign of complex seizures or raised intracranial pressure, or may be iatrogenic.

*Circulation*

Tachycardia, hypotension, altered peripheral pulse volume, cool peripheries and prolonged capillary refill time are all signs of compensated shock that may be present in children with malaria, and may result from hypovolaemia due to vomiting, inadequate fluid intake and fever, often complicated by hypoglycaemia and acidosis.

*Disability*

Impaired consciousness, measured through the AVPU scale or the children’s Glasgow coma scale, may be present. It is important to note the child’s posture and monitor for convulsive movement. If neurological signs are present, it is essential to also consider other diagnoses, such as infection of the central nervous system or intracranial haemorrhage. Glycaemic status must be measured.

**Investigations**

When investigating for malaria, a blood test is required, without delay, to rule-in or rule out the diagnosis. If suspecting malaria in primary care, the patient should be referred to hospital unless rapid malaria testing is available; even then, blood films are required to confirm or exclude the diagnosis.

The gold standard when diagnosing and confirming the diagnosis of malaria is microscopy. This is achieved through the examination of thick and thin blood smears. As well as having the advantage of parasite quantification and species identification, it is highly specific and sensitive. Nevertheless, its advantages are dependent on the availability of experts in laboratories, especially out of hours. In this context, rapid diagnostic tests (RDT), which are able to detect parasitic antigens, are also used despite their lower sensitivity, especially in non-*falciparum* infections. The British Committee for Standards in Haematology guidelines recommend for RDTs to be used in conjunction with blood films and not as a replacement. All patients should have blood films when malaria is suspected.

In the event that the initial blood film is negative, repeat films are warranted 12-24 hours following the initial sample and another sample after a further 24 hours. If a competent microscopist rules out three negative specimens, malaria is unlikely.

Thrombocytopenia is a feature in children with malaria but is not specific. Therefore a full blood count is required and liver function tests, urea and electrolytes and clotting studies need to be performed. A blood gas, to assess for acid-base status is required. Additionally, a G6PD screen, due to the risk of haemolysis following treatment by primaquine for *P.vivax* or *P ovale*, is required prior to initiation of treatment.

Confirmed cases of malaria need to be notified to public health authorities. Furthermore, members of the travelling group/family of the returned traveller with malaria should be informed that they should seek medical attention if they become symptomatic as they have shared the same exposure risk.

**Management**

The treatment of malaria in children is dependent on the species involved (*P. falciparum* or non-falciparum) and on the severity/complications (uncomplicated malaria or severe and complicated malaria). It is essential to counsel the patient and their relatives once the diagnosis is confirmed (Box 3).

**Uncomplicated falciparum malaria**

All children, with confirmed *P falciparum* malaria need to be admitted to hospital and specialist advice should be sought, owing to the risk of deterioration despite initiation of appropriate treatment, and because of the risk of not tolerating oral therapy.

Artemisinin combination therapy (ACT) is recommended as first line therapy for children in the U.K.. If ACT treatment is not available, an effective alternative in the U.K. is the combination of oral quinine with seven days of clindamycin or doxycycline, for children greater than the age of 12.

**Severe and complicated falciparum malaria**

The clinical signs that indicate a poor prognosis are respiratory distress and impaired consciousness, coma or prostration. Severe anaemia and metabolic complications, such as acidosis and hypoglycaemia, are common in severe malaria (Box 4).

Crucially, the initial management of malaria in a sick child involves the rapid identification of emergency and priority signs. Once identified, it is important to manage the patient in a paediatric intensive care unit or high dependency unit alongside the support of specialist in paediatric infectious disease with an interest in malaria. Fluid resuscitation and correction and monitoring of hypoglycaemia are important. Moreover, as malaria can also mimic severe bacterial sepsis or meningitis, it is essential to treat the patient with broad spectrum antibiotics until a bacterial infection can be ruled out.

The Advanced Paediatric Life Support Group guidelines should be followed when managing seizures in children with malaria. Severe anaemia can be treated with blood transfusions where clinically indicated. A Cochrane review, in the year 2000, stated there is insufficient evidence for *routinely* administering blood to clinically stable children with severe anaemia.

The confirmation of a malaria diagnosis should not delay the emergency management and the initiation of resuscitation treatment. Specific antimalarial drugs can be deferred during transport to hospital, although if the clinical suspicion is high, intravenous (IV) Artesunate should be administered without delay, in line with WHO guidance, for treating severe falciparum malaria. IV Artesunate is preferred over IV quinine, however if IV artesunate is not immediately available, treatment should not be delayed and IV quinine is indicated.

**Non-falciparum malaria**

*P vivax* and *P ovale* are the two species that can cause infection relapses weeks to months following the initial and primary infection, even if this was successfully treated. Relapse is due to the re-animation of parasites (hypnozoites) that have persisted in a dormant state in the liver. Therefore, the aim of treatment is to target both the blood and liver stages of infection at the time of the initial treatment. To treat the blood forms of non-falciparum infections an oral ACT or a chloroquine can be used. Although chloroquines are very effective against *P malariae, P ovale,* and *P.knowlesi* and most cases of *P* vivax, ACT therapy should be first-line if falciparum infection cannot be ruled out or there is a mixed infection. Artesunate or quinine should be administered intravenously for cases of severe or complicated non-falciparum infections. Primaquine is the drug of choice to prevent relapse, although alternative drugs are becoming available. Primaquine, which must be taken daily for 2 weeks, should be used only after a test of the patient’s G6PD status, as the drug may cause severe haemolysis in G6PD-deficient subjects.

**Prevention of Malaria**

The main approach to prevent malaria and reduce transmission is through vector control. Insecticide treated mosquito nets and indoor residual spraying of insecticides are the two forms of vector control most effective in a wide range of circumstances.

If practical, attempt to cover children, if outdoors after sunset, with loose-fitted clothes, long sleeves, long trousers and socks, to minimise access to the female anopheles mosquito to skin. Additionally, air-conditioning reduces the likelihood of being bitten due to the low night time temperature.

Chemoprophylaxis is recommended if appropriate for the destination and the individual. It is therefore essential to perform a stringent risk assessment, which includes a clinical history, past medical history, current medication and allergies, before a trip to an endemic area is planned.

**Summary**

Symptoms of malaria can often be non-specific and as malaria is a medical emergency, children with suspected malaria should be assessed and evaluated immediately. A careful travel and exposure history needs to be obtained. If the clinical suspicion is high or if malaria is confirmed, it is essential to request for specialist help with clinical management.

**Further reading:**

1. WHO. World Malaria Report. 2019.

2. Public Health England . Malaria imported into the United Kingdom: 2018 Implications for those advising travellers. 2019; Available from: www.facebook.com/PublicHealthEngland

3. Crawley J, Chu C, Nosten F, Mtove G. Malaria in children. Lancet [Internet]. 2010;375(9724):1468–81.Available from: http://dx.doi.org/10.1016/S0140-6736(10)60447-3

4. Bartoloni A, Zammarchi L. Clinical aspects of uncomplicated and severe malaria. Mediterr J Hematol Infect Dis. 2012;4(1).

5. Bailey JW, Williams J, Bain BJ, Parker-Williams J, Chiodini PL. Guideline: The laboratory diagnosis of malaria. Br J Haematol. 2013;163(5):573–80.

6. Brabin B, Ganley Y. Imported malaria in the UK. Arch Dis Child. 1997;77:76–81.

7. Lalloo DG, Shingadia D, Bell DJ, Beeching NJ, Whitty CJM, Chiodini PL. UK malaria treatment guidelines 2016. J Infect. 2016;72(6):635–49.

8. Advanced Life Support Group. Advanced Paediatric Life Support: A practical approach to emergencies. 6th Editio. 2016.

9. Chiodini, Patel D, Whitty C. Guidelines for malaria prevention in travellers from the United Kingdom, 2019. London Public Heal Engl. 2019;

Severe or complicated malaria in children:

* Impaired consciousness or seizures
* Respiratory distress or acidosis (pH < 7.3)
* Hypoglycaemia (2.2 mmol/l)
* Severe anaemia (<8g/dl)
* Prostration
* Parasitaemia > 2% red blood cells parasitized

Box 1 – Symptoms and signs of severe or complicated malaria in children

**Malaria cases that travelled abroad from the U.K. included:**

* travel for holiday
* business/professional
* civilian/air crew
* children visiting parents abroad
* armed forces
* Visiting friends and relatives (VFR)

Box 2 – Types of cases and reasons of travel abroad from the U.K.

**What to tell the patient and their family8**

* Reassure that they are not infectious to others
* Inform family that if they were part of the travelling group they need to seek medical attention if symptoms develop due to the exposure risk.
* Inform family that as part of routine national policy, the relevant public health authorities will be notified
* If fever recurs despite treatment of malaria, to report to their general practitioner
* Provide information on sources of advice to ensure they have up-to-date information on the prevention of malaria for future travels. It is important to reinforce this.

Box 3 – What to tell the patient and their family/guardian if they are positive for malaria.

**Factors affecting incubation period:**

* The species of infecting parasites
* Transmission method
* Degree of previous immune state of the host
* The use of chemoprophylaxis
* The density of parasite inocula

Box 4 – Factors affecting incubation period