Review of UK malaria treatment guidelines 2016 (Public Health England Advisory Committee on Malaria Prevention in UK Travellers)

Ceri Evans,[1,2] Felicity Fitzgerald,[3,4] Aubrey J. Cunnington[4,5]

[1]Zvitambo Institute for Maternal and Child Health Research, Harare, Zimbabwe
[2]Blizard Institute, Queen Mary University of London, London, UK
[3]Infection, Immunity and Inflammation, UCL Great Ormond Street Institute of Child Health, London, UK
[4]Department of Paediatric Infectious Diseases, St. Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK
[5]Section of Paediatrics, Imperial College London, London, UK

Corresponding author: Dr. Felicity Fitzgerald PhD, Infection, Immunity and Inflammation, UCL Great Ormond Street Institute of Child Health, London, UK; felicity.fitzgerald@ucl.ac.uk

Words: 1324
Boxes: 3
References: 8

Information about current guideline

This guideline covers the diagnosis and management of malaria, and was published in the Journal of Infection in June 2016.[1] It was written by the Public Health England Advisory Committee on Malaria Prevention (PHE ACMP) based on review of available evidence and expert consultation (using a modified GRADE criteria for assessment of evidence and strength of recommendation), to be in line with World Health Organization guidelines on management of malaria.[2] It relates to malaria in both adults and children in the UK although here we focus on the diagnosis and management of children returning to the UK with suspected malaria. Malaria is the most common imported tropical pathogen in the UK, and children comprise about 10% of the 1300-1800 UK cases per annum. *Plasmodium falciparum* is by far the most common (around 75% of cases) and is associated with more severe disease.

Previous guideline

This guideline replaces the previous PHE ACMP UK malaria treatment guideline (2007),[3] and suggested guidance/recommendations from Maitland *et al.* (2005), which advocated more aggressive fluid resuscitation in severe malaria than now suggested.[4]

RESOURCES (BOX)

- http://www.journalofinfection.com/article/S0163-4453(16)00047-5/fulltext Full guideline
- https://www.ncbi.nlm.nih.gov/pubmed/26880088 Executive summary
- http://apps.who.int/iris/bitstream/10665/162441/1/9789241549127_eng.pdf?ua=1&ua=1 World Health Organization (WHO) guidelines for the treatment of malaria (2015)
- https://www.gov.uk/government/publications/malaria-prevention-guidelines-for-travellers-from-the-uk Public Health England malaria prevention guidelines
- http://travelhealthpro.org.uk Country-specific information on malaria
- www.fitfortravel.nhs.uk Public access website providing health information for people travelling abroad from the UK

Key issues that the guideline addresses

When to suspect malaria?

Malaria should be considered in any unwell or feverish child who has visited an endemic country regardless of whether prophylaxis was taken. *P. falciparum* usually presents within 1 month of exposure (minimum 6 days), although later presentations can occur. Other species may present over a year post-travel.

Clinical Features

Malaria in children can be notoriously non-specific, even without fever. Although fever, malaise and lethargy are the most common symptoms, children can present with gastrointestinal symptoms (including diarrhoea), jaundice, breathing difficulties or sore throat. Examination may reveal hepato- and/or splenomegaly and lethargy.

Diagnosis

Thick and thin blood films remain the gold standard for detection and speciation of malarial parasites, but rapid diagnostic tests (RDTs) are almost as accurate for *P. falciparum* and *P. vivax.* If there is ongoing clinical suspicion with negative blood films, these should be repeated at 12-24 hours and again after a further 24 hours, particularly if fever is persistent. Empirical therapy in the context of negative tests should only be given with symptoms of severe malaria and on expert advice. Thrombocytopaenia is common in children with malaria; although not diagnostic, it should increase the index of suspicion.

Treatment

Even in uncomplicated malaria, with *P. falciparum* there can be rapid deterioration during the first 24 hours of treatment, so admission is recommended initially. Uncomplicated *P. falciparum* malaria should be treated with oral artemisinin combination therapy (ACT), e.g. artemether-lumefatrine

dosed according to weight (see BNF or Box 8 of guideline [1]). Admission will also ensure that the oral ACT is tolerated as some children can vomit.

Features of severe malaria are:

1. Cerebral malaria
2. Respiratory distress/metabolic acidosis
3. Severe anaemia
4. Prostration (a child unable to sit if normally able to do so, or the inability to drink in a younger child)
5. Hypoglycaemia
6. Electrolyte disturbance
7. Circulatory shock

Severe malaria should be managed in a paediatric intensive care or high dependency unit with advice from a paediatric infectious diseases specialist with malaria expertise. Intravenous artesunate gives a clear survival advantage over quinine and is the drug of choice.[5] Following the results of the FEAST trial showing a detrimental effect of fluid boluses, fluid resuscitation should be cautious even in the context of shock.[6] Glucose monitoring is crucial, and broad spectrum antibiotics should be given until bacterial co-infection is excluded.

For non-*P. falciparum* malaria, both ACT and chloroquine are effective for acute infection, although there is growing resistance to chloroquine in some Indonesian areas. ACT may clear parasites faster and covers for *P. falciparum* in case mixed infection cannot be excluded. To prevent relapse for *P. vivax* and *P. ovale,* primaquine treatment should overlap with ACT to ensure eradication of hypnozoites in the liver, after exclusion of G6PD deficiency.

All children receiving intravenous artesunate need a repeat full blood count at 2 weeks post-therapy as it is associated with delayed haemolysis. Families should be informed about mandatory notification of Public Health England, reassured that the child is not infectious to others (although other

family members who also travelled may be at risk), and informed that relapse/recrudescence is a risk, and so medical attention should be sought with recurrent fevers. Finally, they should be directed to seek up to date advice on malarial prevention when travelling in future (see *Resources* box).

UNDERLYING EVIDENCE BASE (BOX)

- Dondorp AM, Fanello CI, Hendriksen IC, et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. *Lancet* 2010;376:1647-57.[5]
- Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med* 2011;364:2483-95.[6]
- Meremikwu M, Smith HJ. Blood transfusion for treating malarial anaemia. *Cochrane Database of Syst Rev* 2000:CD001475.[7]

What do I need to know?

What should I start doing?

1. Use intravenous artesunate instead of quinine for treatment of severe malaria [5]
2. If intravenous artesunate is not immediately available, do not delay initiating treatment with intravenous quinine
3. Use artesunate combination therapy (ACT) orally as first line treatment for uncomplicated malaria (both *P. falciparum* and non-*P. falciparum*)

What should I not do?

- Do not give rapid fluid boluses. For patients with shock, cautious and slow volume resuscitation should be used – the FEAST trial found an increased risk of death in children receiving crystalloid or colloid fluid boluses.[6]
- Do not give routine blood transfusions except in severe anaemia, as they can increase adverse events without reducing mortality.[7]

What should I continue doing as before?

- Malaria should be suspected in anyone with a history of fever and return from a malaria endemic area even if prophylaxis was taken
- Thick and thin blood smears are still the gold standard for diagnosis
- Rapid diagnostic tests (RDT) detect parasite antigens, and are a useful addition to blood smears but can miss non-*P. falciparum* malaria
- If there is ongoing clinical suspicion of malaria but the initial blood films are negative, two further films should be assessed
- All children with malaria should have at least 24 hours of inpatient observation
- Severe or complicated malaria should be managed in an intensive care or high dependency setting, with support from a paediatric infectious diseases specialist
- Broad spectrum antibiotics should be used in addition to anti-malarial treatment until bacterial co-infection has been excluded
- Notify all malaria cases to Public Health England
- Remember eradication of liver stage hypnozoites with primaquine in *P. vivax* and *P. ovale* malaria

Unresolved controversies

1. *Potential management of uncomplicated malaria as an outpatient*

Adults with *P. ovale, P. vivax* and *P. malariae* are often managed in an outpatient setting, and in specialist centres *P. falciparum* is sometimes managed in outpatients by experienced clinicians with clear protocols. In children, at least 24 hours of observation in hospital is recommended due to the risk of rapid deterioration and vomiting ACT. Data are currently lacking around the potential safety of more rapid discharge in the UK context.

2. *Three films to exclude malaria*

The evidence underlying the requirement of three negative films over a 36-48 hour period to exclude malaria has recently been reviewed by Wilson *et al.*[8] Most published literature relates to adult data, but the combination of one blood film and one RDT is extremely sensitive for malaria. The authors

concluded that it is safe to exclude malaria in a well-appearing, afebrile child with one negative RDT in addition to one negative blood film, although appropriate safety netting advice should be provided.[8]

3. Definition of severe malaria in non-endemic countries

The precise definitions of severe malaria, which predict morbidity or mortality, and which justify PICU admission or additional interventions such as blood transfusion, are not based on firm evidence from non-endemic populations. For example, whether a 2% parasitaemia in a child with otherwise uncomplicated malaria justifies PICU/HDU admission is widely debated. It is worth noting that the WHO guideline [2] has a more extensive list of severity features, including renal impairment, which is a strong predictor of death in African settings, and the addition of base excess <-8mEq/L or lactate >5mmol/L to the definition of acidosis. However, the relative importance of these features in the non-endemic setting remains unclear; the threshold for admission to PICU/HDU is likely to be dependent on the experience of the particular unit of managing malaria in children in the UK.

CLINICAL BOTTOM LINE (BOX)

- Malaria should be suspected in all children with fever and travel to a malaria endemic region
- Children with severe/complicated malaria should be managed in an intensive care/high dependency setting
- Intravenous artesunate should preferentially be used to treat severe/complicated malaria, and oral ACT for non-severe cases
- Broad spectrum antibiotics should be used until bacterial co-infection has been excluded
- Fluid resuscitation should be cautious

Declarations and Funding

We declare we have no conflicts of interest. Ceri Evans is supported by the Wellcome Trust (203905/Z/16/Z). Felicity Fitzgerald is supported by the

National Institute for Health Research and the National Institute for Health Research Biomedical Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London. Aubrey Cunnington is supported by an MRC Clinician Scientist Fellowship.

References

1. Lalloo DG, Shingadia D, Bell DJ, et al. UK malaria treatment guidelines 2016. *J Infect* 2016;72:635-49.
2. World Health Organization. Guidelines for the treatment of malaria. Third ed. Geneva: World Health Organization; 2015.
3. Lalloo DG, Shingadia D, Pasvol G, et al. UK malaria treatment guidelines. *J Infect* 2007;54:111-21.
4. Maitland K, Nadel S, Pollard AJ, et al. Management of severe malaria in children: proposed guidelines for the United Kingdom. *BMJ (Clinical Research Ed)* 2005;331:337-43.
5. Dondorp AM, Fanello CI, Hendriksen IC, et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. *Lancet* 2010;376:1647-57.
6. Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med* 2011;364:2483-95.
7. Meremikwu M, Smith HJ. Blood transfusion for treating malarial anaemia. *Cochrane Database of Syst Rev* 2000:CD001475.
8. Wilson IE, Shingadia D, Yeung S, et al. Question 2: Are three malaria tests necessary in children returning from the tropics with fever? *Arch Dis Child 2018;103:1-3.*