Diagnosis and initial management of malaria

Malaria is a life-threatening disease caused by several species of protozoan parasites in the *Plasmodium* genus. It is transmitted by the female *Anopheles* mosquito in tropical and subtropical regions, resulting in 212 million cases and 429 000 deaths in 2015 alone (World Health Organization, 2013, 2016). The UK saw a total of 1400 imported malaria cases in 2015, although an additional 44% are estimated to be unreported (Public Health England, 2016). UK deaths from imported malaria have been in single figures for the past decade, with an annual average of six deaths.

Three quarters of cases in the UK are caused by *Plasmodium falciparum*, the most severe form of malaria, followed in order of frequency by *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi* (Public Health England, 2016). Infection with *P. vivax* and *P. knowlesi* may in some cases result in severe disease. *P. falciparum* is the dominant malarial species in sub-Saharan Africa, the region with the highest burden of malaria globally. *P. vivax* is the most common species outside of Africa. Interestingly, *P. ovale* has recently been subdivided into two different species (*P. o. curtisi* and *P. o. wallikeri*), which circulate simultaneously in African populations, although potential differences in their clinical presentation or treatment response are not yet known (Oguike et al, 2011).

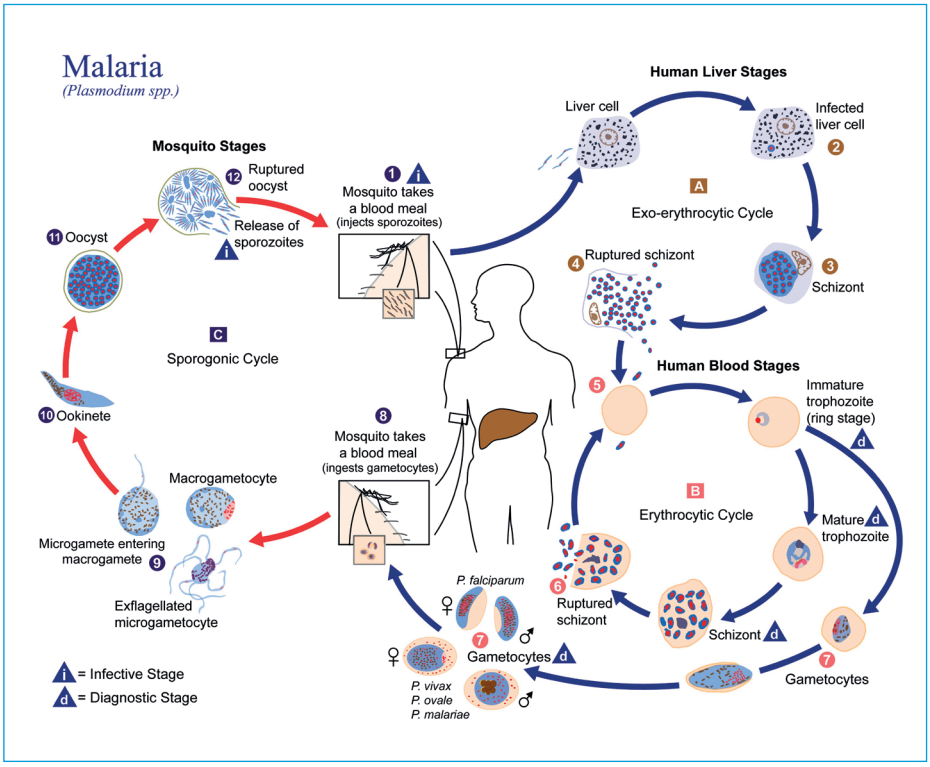
Malaria Reference Laboratory data show that 64.5% of imported malaria cases were in patients visiting family in their country of origin (Smith et al, 2008), with a poor uptake of pre-travel prophylaxis. However, deaths are more frequent in returning tourists, the elderly and in those presenting to UK health-care facilities where malaria is rarely encountered and the diagnosis thus delayed (Checkley et al, 2012). Independent risk factors for severe malaria include white or Asian ethnicity and parasitaemias above 2% (Phillips et al, 2009). The vast majority of UK cases are imported from Africa as a whole (82%), with just over half (59%) from west Africa. Most of the remaining cases originate from southern Asia.

Presentation

Most patients will give a history of fever, along with other non-specific symptoms such as headache and malaise. The rupture of parasitized red blood cells coincides with the fever, although the textbook tertiary or quaternary patterns rarely occur in practice and may only emerge once parasite development within red blood cells has synchronized. Trophozoite parasite stages mature within red blood cells to become schizonts which fill the cell. The red blood cell then ruptures, releasing merozoites ready to infect further red blood cells (*Figure 1*).

A careful travel history is vital, including specific localities visited, as endemicity varies significantly within countries, and noting any stopovers on the journey. Information on endemic countries is widely available, the Public Health England commissioned website www.travelhealthpro.org.uk being one reliable resource. Discussion with an infectious disease expert is also advised. The crucial point is to consider the diagnosis in those returning from endemic areas within the last year or more. *P. falciparum* can present from 6 days after exposure, but

Figure 1. Malaria life cycle. Diagram showing the life cycle of the *Plasmodium* spp. parasite that causes malaria. It is transmitted to humans via the bite of an infected female *Anopheles* spp. mosquito. Symptoms include fever and headache, which can proceed to coma and death.



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typically within the first month or two. *P. vivax* and *P. ovale* may present after 6 months to several years, because of the persistence of latent parasites (hypnozoites) in the liver. Remember that the use of prophylaxis does not exclude the diagnosis. Beware the potential pitfalls from misleading symptoms which result in common misdiagnoses such as 'non-specific viral illness', influenza, gastroenteritis and hepatitis (Lalloo et al, 2016).

Where a travel history cannot be obtained and the clinical picture is compatible (e.g. fever, coma and thrombocytopenia with no other localizing features), consider the diagnosis and add a malaria test, as it is cheap and may save a life. While malaria is one of the most common causes of fever in the returning traveller, always consider other common tropical or subtropical infections (e.g. dengue, chikungunya, Zika, rickettsial infections and leptospirosis) and cosmopolitan infections (e.g. urinary tract infections, viral upper respiratory tract infections and soft tissue infections) in the differential diagnoses (Thwaites and Day, 2017).

Most, but not all patients will have an objective fever on presentation. No clinical signs are specific to the diagnosis, although splenomegaly may be highly suggestive in the context of fever and an appropriate travel history (D'Acremont et al, 2002). Jaundice, confusion or seizures may be seen in severe disease (Lalloo et al, 2016).

Features of severity

Severe malaria is defined by the presence of one or more clinical features or abnormal investigation results that are a poor prognostic indicator. Clinical features of severe malaria include impaired consciousness, prostration (debilitating weakness), seizures, acidotic breathing, acute pulmonary oedema, shock, jaundice and abnormal bleeding. Investigation results indicating severe malaria include hypoglycaemia, metabolic acidosis, severe normocytic anaemia, haemoglobinuria, high lactate levels and renal impairment (World Health Organization, 2013). The percentage of parasitized red blood cells is another important indicator of severity, with parasitaemias above 2% in a low prevalence setting such as the UK being treated as severe disease (Lalloo et al, 2016). However, in high prevalence settings much higher parasitaemias are often tolerated (World Health Organization, 2013) and technically most guidelines define severe malaria as parasitaemias above 10% (Lalloo et al, 2016).

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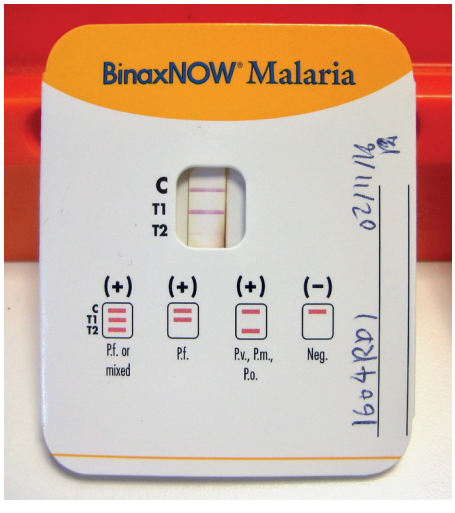
Diagnosis

On routine investigations, thrombocytopenia may be a first (non-specific) clue to a diagnosis of malaria (D'Acremont et al, 2002). Urgent examination of thick and thin blood films is required for all patients with suspected malaria (Lalloo et al, 2016). Thick films enable identification of the presence of parasite and thin films enable parasite speciation and estimation of parasitaemia, which is only relevant in *P. falciparum* infection. After treatment is started, daily blood films are required to ensure parasite clearance, although increasing numbers in the first 24 hours may be expected (as parasitaemias may vary according to the stage of parasite development) and do not indicate treatment failure (Lalloo et al, 2016).

Rapid diagnostic tests have been validated as an adjunct to blood film examination and are particularly useful when an experienced microscopist is unavailable. Both positive and negative results require confirmation with blood films. As shown in *Figure 2*, rapid diagnostic tests can detect and differentiate between both *P. falciparum* and non-falciparum infections by detection of specific *P. falciparum* as well as pan-species antigens (Bailey et al, 2013).

Patients should receive the results of malaria testing on the same day the diagnosis is suspected, because of the potential for rapid deterioration. Most patients should therefore be directed to a hospital, as GP organized tests are unlikely to result in a same-day diagnosis.

Figure 2. Example of a rapid diagnostic test for malaria.



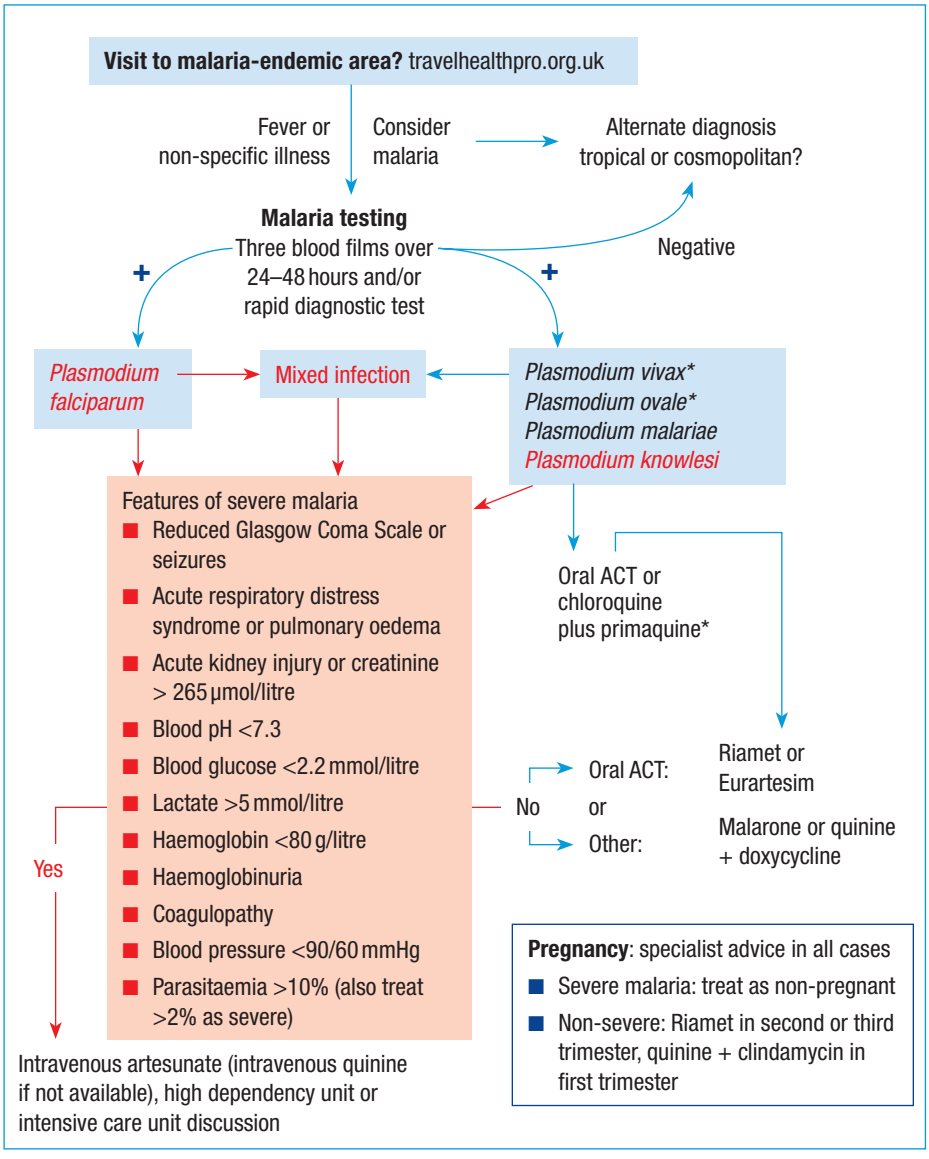
Treatment

The choice of treatment will depend on the severity of disease and the species of malaria. The diagnostic and management process is outlined in *Figure 3*. Discuss with a high dependency or intensive care unit early if there are any features of severity. Most patients will require hospital admission unless they have non-severe disease with species other than *P. falciparum*. Clinical deterioration can occur within the first 24 hours after treatment initiation (Lalloo et al, 2016) and consultation with an infectious disease specialist is generally advised. All pregnant women suspected of having malaria should be discussed with an expert in the field, as not only treatment but also diagnosis can be difficult in this group.

Severe disease

Intravenous therapy is indicated if any features of severity are identified. Intravenous artesunate is the drug of choice as demonstrated in the landmark SEAQUAMAT and AQUAMAT trials by Dondorp et al (2005, 2010), subsequently verified by other trials and a meta-analysis (Sinclair et al, 2012). Artesunate is widely available although currently unlicensed in the UK, thus requiring administration by the prescribing doctor. The dosing of artesunate is not listed in the British National Formulary, but is 2.4 mg/kg intravenous injection at 0, 12 and 24 hours then daily thereafter. A minimum of three doses should be given, with a 5-day maximum course. Once the patient has sufficiently recovered

Figure 3. Malaria diagnostic and management flowchart with reference to infecting species and features of severity. ACT = artemisinin-based combination therapy. *check glucose-6-phosphate dehydrogenase. Adapted from World Health Organization (2013), Lalloo et al (2016).



to have oral treatment, a full course of artemisinin-based combination therapy should be commenced, examples of which are outlined below (dosing as per the British National Formulary).

Note that significant late haemolysis occurs in up to 15% of patients treated with intravenous artesunate, often after 7–14 days, requiring appropriate follow-up monitoring with full blood counts (Rehman et al, 2014). Intravenous quinine along with oral doxycycline (or clindamycin in pregnancy or childhood) is an alternative if artesunate is not immediately available, with mandatory monitoring for arrhythmias and hypoglycaemia (2-hourly bedside blood glucose measurement).

Fluid administration should proceed with extreme caution, as pulmonary oedema and acute respiratory distress syndrome commonly complicate malaria, even in the state of vascular depletion. Hanson et al (2013) demonstrated that high lactate levels in patients with malaria are predictive of death. Lactic acidosis did not respond to fluid resuscitation in this study as it was caused by parasite sequestration in capillaries, rather than pure hypovolaemia as in sepsis. Also note that shock may indicate concurrent sepsis from bacterial infection (termed 'algid malaria'), indicating broad-spectrum antibiotics along with antimalarials (Lalloo et al, 2016).

KEY RESOURCES

Useful contacts after discussion with local expert (UK only):

- The Hospital for Tropical Diseases, London: 02034567890
- Tropical and Infectious Disease Unit, Liverpool: 01517062000
- Public Health England Imported Fever Service: 08447788990

Lalloo et al (2016) https://doi.org/10.1016/j.jinf.2016.02.001

Thwaites and Day (2017) https://doi.org/10.1056/NEJMra1508435

Information on malaria-endemic countries: travelhealthpro.org.uk/

Non-severe *P. falciparum*

Artemisinin-based combination therapies are now the treatment of choice for all non-severe cases of *P. falciparum*, most commonly in the form of artemether–lumefantrine (Riamet) in the UK. Oral quinine is still available as an alternative, although this is less well tolerated and requires a second drug to protect against resistance. Atovaquone–proguanil (Malarone) is another commonly used non-artemisinin-based combination therapy alternative. Reports of artemisinin-based combination therapy resistance and resulting treatment failures in south-east Asia, plus isolated reports in Africa (Lu et al, 2017), while alarming do not yet necessitate deviation from these recommendations as per the British Infection Association guidelines (Lalloo et al, 2016). As demonstrated by Sharma et al (2016), there is increasing evidence that selected patients presenting with non-severe falciparum malaria can be managed on an outpatient basis.

Non-falciparum

Most non-falciparum species remain susceptible to chloroquine. An artemisinin-based combination therapy such as Riamet is indicated if there is any doubt about the species, if there is mixed infection, or if the patient was in an area where chloroquine resistance to *P. vivax* is common. *P. vivax* or *P. ovale* form hypnozoites in the liver which are responsible for relapses months to years later if not eradicated with primaquine. Check glucose-6-phosphate dehydrogenase status beforehand, as those who are deficient may suffer severe haemolysis if given primaquine.

Note that the rare species *P. knowlesi* has the appearance of *P. malariae* on the blood film, but the latter does not cause severe disease while the former may be life threatening. Looking for signs of severe disease in all cases of malaria will ensure that the patient is managed appropriately.

Conclusions

Malaria causes a vast number of infections and deaths in the tropics, and is one of the commonest causes of imported fever to the UK. However, the relatively few cases seen in many UK centres results in uncertainty and delays in the diagnosis and management of this potentially life-threatening infection. Malaria is a diagnosis not to miss, and the recognition of severe malaria at presentation will enable early initiation of life-saving treatment. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Consider malaria in the returning traveller with fever or non-specific symptoms.
- Request urgent blood films for malaria, and a further two if suspicion remains despite initial negative results.
- Consultation with an expert in infection is advised (see *key resources*).
- The patient with *Plasmodium falciparum* can rapidly deteriorate in the first 24 hours, so admission is advised.
- Look for features of severe infection in all cases of malaria.
- Intravenous artesunate is the treatment of choice for severe malaria, but give intravenous quinine if delays are expected.
- Artemisinin-based combination therapies are the treatment of choice for all species of non-severe malaria, commonly Riamet.
- Caution with use of fluids is advised.