

## 6 - Special Groups (Medical Conditions)

<b>6.1</b>	Smoking cessation.	65
<b>6.2</b>	Pregnancy.	65
<b>6.3</b>	Breastfeeding.	66
<b>6.4</b>	Anticoagulants .	66
<b>6.5</b>	Epilepsy.	67
<b>6.6</b>	Glucose 6-phosphate dehydrogenase deficiency.	67
<b>6.7</b>	Sickle Cell disease.	68
<b>6.8</b>	Immunocompromised Travellers. <i>Risks for transplant patients</i> <i>Risks for HIV/AIDS patients</i>	68
<b>6.9</b>	Liver disease.	69
<b>6.10</b>	Renal impairment.	69
<b>6.11</b>	Splenectomy.	70
<b>6.12</b>	Acute porphyrias.	70



## 6 Special Groups (Medical Conditions)

### 6.1 Smoking cessation

Chloroquine or mefloquine should not be used in those taking Zyban® (bupropion hydrochloride SR) as the chances of seizure may be increased.

### 6.2 Pregnancy

Pregnant women are advised to avoid travel to malarious areas.

In the event that travel is unavoidable, the pregnant traveller must be informed of the risks which malaria presents and the risks and benefits of antimalarial chemoprophylaxis.

Pregnant women have an increased risk of developing severe malaria and a higher risk of fatality compared to non-pregnant women.

Diagnosis of falciparum malaria in pregnancy can be particularly difficult as parasites may not be detectable in blood films due to sequestration in the placenta.

Expert advice is required at an early stage if malaria is suspected in a pregnant woman. Complications, including severe haemolytic anaemia, hypoglycaemia, jaundice, renal failure, hyperpyrexia and pulmonary oedema, may ensue. The result may be miscarriage, premature delivery, maternal and/or neonatal death.

Congenital malaria is rare, but occurs more commonly with *Plasmodium vivax* than with the other malaria parasites of humans.

Avoidance of mosquito bites is extremely important in pregnancy as pregnant women are particularly attractive to mosquitoes. Ideally, pregnant women should remain indoors between dusk and dawn. If they have to be outdoors at night they should adhere rigorously to bite precautions (see chapter 3).

DEET should be used in a concentration of not more than 50%. DEET has a good safety record in children<sup>16</sup> but ingestion should be avoided. Nursing mothers should wash repellents off their hands and breast skin prior to handling infants. See Chapter 3 for further details on DEET.

- Chloroquine and proguanil: safe in all trimesters of pregnancy. Their major disadvantage is the relatively poor protection they give in many geographical areas due to the presence of drug-resistant *P. falciparum*. Pregnant women taking proguanil should receive supplementation with 5 mg folic acid daily.
- Mefloquine: caution advised (see below).
- Doxycycline: contraindicated in pregnancy.
- Atovaquone/proguanil: lack of evidence on safety in pregnancy.

The long-term traveller guidelines<sup>55</sup> describe the evidence for prescribing mefloquine during pregnancy. Briefly, it seems unlikely that mefloquine is associated with adverse foetal outcomes. There is no strong association between mefloquine in treatment doses<sup>56,57</sup>, and stillbirths or miscarriages in the second and third trimesters although a lack of data on its use in the first trimester has encouraged caution. The decision whether or not to advise mefloquine prophylaxis in pregnancy therefore requires a careful risk-benefit analysis. Where the levels of transmission and drug resistance (see country tables in chapter 4) make mefloquine an agent of first choice it is generally agreed that mefloquine may be advised in the second and third trimesters of pregnancy. Given the potential severity of falciparum malaria in a pregnant woman, its use may also be justified in the first trimester in areas of high risk of acquiring falciparum malaria such as sub-Saharan Africa, after taking expert advice (see chapter 9).

Women who have taken mefloquine inadvertently just prior to or during the first trimester should be advised that this does not constitute an indication to terminate the pregnancy.

### **Chemoprophylaxis prior to conception**

If a female traveller is planning to conceive during a visit to a destination with a high risk of contracting chloroquine-resistant falciparum malaria, expert advice should be sought (see chapter 9 for advice centres).

Time to allow after finishing a course of an antimalarial before attempting to conceive:

- Mefloquine: 3 months.
- Doxycycline: 1 week.
- Atovaquone/proguanil: 2 weeks.

### **6.3 Breastfeeding**

- Mefloquine: experience suggests safe to use during lactation.
- Doxycycline: contraindicated (do not use).
- Atovaquone/proguanil: not recommended because of the absence of data however, can be used when breast-feeding if there is no suitable alternative antimalarial.

Nursing mothers should be advised to take the usual adult dose of antimalarial appropriate for the country to be visited.

The amount of medication in breast milk will not protect the infant from malaria. Therefore, the breastfeeding child needs his or her own prophylaxis, which for children of breastfeeding age will be either chloroquine plus proguanil or mefloquine. Atovaquone/proguanil may be used if the child weighs 11kg or more.

### **6.4 Anticoagulants**

Travellers who take anticoagulants should ensure their INR (International Normalised Ratio) or clotting time is stable prior to departure.

Patients on warfarin may have underlying cardiovascular disease and may be on cardiovascular medication. Interactions with other medication together with the

individuals' medical history should be taken into account when deciding on appropriate malaria chemoprophylaxis.

- Chloroquine: no interaction between warfarin and chloroquine documented in the BNF, although there is a caution in the SPC for Nivaquine.
- Proguanil: an isolated report of an enhanced effect of warfarin when taken together with proguanil<sup>58</sup>.
- Mefloquine: not considered to be a problem for those taking warfarin. The manufacturer states that 'although no drug interaction is known with anticoagulants, effects of mefloquine on travellers should be checked before departure.' Please see below for how this can be monitored.
- Doxycycline: the anticoagulant effect of coumarins (including warfarin) is possibly enhanced by tetracyclines<sup>59</sup>.
- Atovaquone / proguanil: unknown whether there are interactions between atovaquone/proguanil and warfarin, although there have been isolated reports of an enhanced effect of warfarin when taken together with proguanil (see above under proguanil).

Advice for travelers needing malaria chemoprophylaxis who are taking warfarin:

- Travellers should start taking their malaria tablets more than 1 week (and ideally 2-3 weeks in the case of mefloquine) prior to their departure.
- A baseline INR should be checked prior to starting chemoprophylaxis, and re-checked after 1 week of taking chemoprophylaxis.

- If a traveller is away for a long period of time the INR should be checked at intervals at the destination. (However, the sensitivity of thromboplastin reagent used by some laboratories in different countries may vary<sup>60</sup>).
- Once chemoprophylaxis has been completed, the INR should be checked again to re-stabilise anticoagulant therapy.

### 6.5 Epilepsy

Proguanil alone (200 mg daily) is recommended for malarious areas without chloroquine resistance. For areas with a high risk of chloroquine-resistant malaria, such as sub-Saharan Africa, doxycycline or atovaquone/proguanil can be used.

- Chloroquine: unsuitable.
- Mefloquine: unsuitable.
- Doxycycline: half-life may be reduced by phenytoin, carbamazepine, and barbiturates, so in theory its dose should be increased for patients taking these drugs. However, there is currently no direct evidence that this is necessary.

### 6.6 Glucose 6-phosphate dehydrogenase deficiency

Glucose 6-phosphate dehydrogenase (G6PD) is an enzyme that helps protect the red cell against oxidative damage. Absence of G6PD renders the red cell liable to haemolysis in the presence of some drugs.

All G6PD-deficient travellers to malarious areas should take appropriate chemoprophylaxis despite some protection against infection being conferred by the most common G6PD deficiency allele in Africa (G6PD A-)<sup>61</sup>.

Chloroquine: theoretical risk of haemolysis in some G6PD-deficient individuals. Haemolysis does not appear to be a problem when chloroquine is given in the dose recommended for malaria chemoprophylaxis so there is no need to withhold chloroquine prophylaxis from those known to be G6PD-deficient. This risk is acceptable in acute malaria<sup>59</sup> and G6PD levels are not usually checked before using chloroquine in treatment doses.

Primaquine: not currently recommended as a first line agent for malaria prevention in UK travellers, but may be considered in special circumstances on expert advice<sup>27</sup>. There is a definite risk of haemolysis in G6PD-deficient individuals. The traveller's G6PD level must be checked before primaquine is prescribed: G6PD deficiency contraindicates its use for prophylaxis.

## 6.7 Sickle Cell disease

Presence of the sickle cell trait confers some protection against malaria, though individuals with the sickle cell trait still require antimalarial prophylaxis.

For those with homozygous sickle-cell disease, malaria is regarded as a significant cause of morbidity and mortality, producing further haemolysis against the background of that due to sickle-cell disease itself<sup>62</sup>. Therefore, it is essential that individuals with sickle-cell disease travelling to malaria-endemic areas receive rigorous antimalarial protection.

## 6.8 Immunocompromised travellers

### 6.8.1 Risks for transplant patients

A review on the prevention of infection in adult travellers after organ transplantation<sup>63</sup> recommended that ciclosporin levels should be monitored if chloroquine is co-administered.

### 6.8.2 Risks for those with HIV/AIDS

All of the HIV protease inhibitors (PIs) in current use, as well as the non-nucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine and efavirenz, interact with the same liver enzymes which metabolise most drugs used for malaria prophylaxis and treatment. This can result in altered metabolism of antimalarials or antiretrovirals, though the extent of this and the clinical significance is often unclear. The prescriber should check on an individual agent basis.

The extra risk of increased severity if malaria is contracted by an HIV-infected traveller is unclear. Most reported studies have been done in those living in endemic areas where HIV infection increases the risks for contracting and developing severe malaria and increasing immunosuppression reduces treatment success<sup>64</sup> although this varies by area<sup>65</sup>. Co-infected pregnant women are at risk from higher parasite density, anaemia and malarial infection of the placenta. Children born to women with HIV and malaria infection have low birth weight and are more likely to die during infancy. It is unclear whether malaria during pregnancy increases the risk of mother-to-child transmission of HIV<sup>66</sup>.

### 6.9 Liver disease

Most antimalarial drugs are excreted or metabolised by the liver. Thus, there is a risk of drug accumulation in severe liver impairment.

- Severe liver disease: all antimalarial drugs are contraindicated, with the possible exception of atovaquone plus proguanil.
- Moderate impairment: proguanil, or atovaquone plus proguanil or mefloquine may be used.
- Mild impairment: chloroquine, or proguanil, or chloroquine plus proguanil, or atovaquone plus proguanil or mefloquine may be used. Doxycycline should be used only with caution.

The choice of chemoprophylaxis should be made after discussion with the patient's specialist, who will be able to assess their degree of hepatic impairment. The Child-Pugh classification

is often used for grading liver function and can be found at <http://www.emea.europa.eu/pdfs/human/ewp/233902en.pdf>

### 6.10 Renal impairment

Chloroquine is partially excreted via the kidneys while proguanil is wholly excreted via the kidneys.

- Chloroquine: dose reduction for prophylaxis is required only in severe renal impairment.
- Proguanil: should be avoided or the dose reduced as shown in table 15. Not to be used in patients receiving renal dialysis.
- Atovaquone/proguanil: not recommended for patients with a creatinine clearance of less than 30mL/minute<sup>59</sup>. Not to be used in patients receiving renal dialysis.

Doxycycline or mefloquine may be used in severe renal failure. There is no need to reduce the dose of mefloquine in renal dialysis<sup>59</sup>.

TABLE 15 DOSES OF PROGUANIL IN ADULTS WITH RENAL FAILURE

RENAL IMPAIRMENT GRADE	SERUM CREATININE $\mu$ MOL/LITRE	CREATININE CLEARANCE ML/MIN/1.73M <sup>2</sup>	PROPHYLACTIC DOSAGE OF PROGUANIL
(none)	<150	$\geq 60$	200mg daily (standard dose)
mild	150-300	20-59	100mg daily
moderate	300-700	10-19	50mg every second day
severe	>700	<10	50mg once weekly

### 6.11 Splenectomy

Those who have no spleen or whose splenic function is severely impaired are at particular risk of severe malaria and, where possible, should avoid travel to malarious areas.

If travel is essential, every effort should be made to avoid infection by rigorous use of antimosquito precautions and strict adherence to appropriate chemoprophylaxis. If the traveller becomes unwell during or after their visit, medical attention is required as a matter of urgency, as malarial parasitaemia in asplenic individuals may rise rapidly to very high levels (e.g. greater than 50% with *P.falciparum*).

### 6.12 Acute porphyrias

Doxycycline is unsafe in porphyria<sup>59</sup> so should not be used for antimalarial chemoprophylaxis in patients with acute porphyria.