MALARIA: PROPHYLAXIS AND THERAPY

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ABSTRACT

Malaria remains a significant cause of morbidity and mortality in many regions of the world. In Singapore, an average of 200 cases of malaria have been reported annually, the majority of which are imported cases. Malaria eradication is a goal that may not be achieved. A more realistic aim is to educate and protect individual travellers. This paper attempts to summarise various therapeutic options including the use of monotherapy and combination therapy. The decision on therapy depends on several factors, such as the Plasmodium species, risk of transmission of the resistant parasite and the severity of infection. So far, none of the chemoprophylactic regimens available can provide an absolute protection from malaria transmission. Therefore, one needs to assess the risk of transmission against the potential risk of adverse drug reaction. Complications of anti-malaria drugs may range from minor cutaneous manifestations to death. General measures to prevent vector transmission of the disease should be emphasised while awaiting the development of an effective malaria vaccine.

Keywords: malaria, prophylaxis, treatment, vaccine, travel

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INTRODUCTION

Malaria is estimated to have a worldwide prevalence in excess of 100 million cases annually. It is associated with approximately 1 million deaths per year in Africa alone[1,2]. Transmission occurs in large areas of central and South America, Africa, India, Southeast Asia, the Middle East, and Oceania[3]. Annually, an average of 200 cases of malaria have been reported in Singapore. In 1990, 216 imported cases were reported. There were three deaths due to falciparum malaria that year[4].

Four protozoan species of the genus *Plasmodium: P. falciparum, P. vivax, P. ovale* and *P. malariae* commonly infect humans. *P. falciparum* infection, especially the multi-drug resistant strains, has been associated with lethal outcomes. Chloroquine-resistant *P. falciparum* (CRPF) is now found in most of the malarious tropics. However, in the Caribbean north of the Panama Canal, in North Africa, the Middle East, some parts of India and South East Asia chloroquine can still be reliably used for the treatment of falciparum infection[5]. Recently chloroquine-resistant *P. vivax* was identified in Indonesia and Papua New Guinea[6,7].

Prevention of malaria

The risk of malaria transmission varies markedly. The intensity of transmission in urban and rural areas within the same region may differ dramatically. Due to the nocturnal feeding habits of *Anopheles* mosquitoes, travellers who spend considerable amount of time in the evening or at night in endemic regions will have a higher risk of acquiring malaria. In view of the possible lethal complications, all travellers to malaria endemic areas are advised to consult a physician regarding the appropriate chemoprophylactic regimen and personal protective measures to prevent malaria. They should also be made aware that regardless of the methods employed, malaria infection may still occur. Symptoms usually begin 8 to 14 days after exposure in a malaria-endemic area but occasionally symptoms may develop several months later[8,9]. Individuals with symptoms should seek medical attention promptly. It should be stressed that delaying therapy in *P. falciparum* infection can be fatal.

In theory, percutaneous introduction of a single *P. falciparum* sporozoite can produce a fatal infection. Travellers must be advised of the importance of measures to reduce contact with mosquitoes.

These include remaining in well-screened areas during mosquito feeding hours between dusk and dawn, using mosquito nets even if the room is screened, wearing light coloured clothes that cover most of the body and to apply insect repellents containing N, N-diethylmetatoluamide (DEET) to exposed skin and clothing when going outdoors[8,9].

None of the anti-malaria chemoprophylactic regimens is totally effective in the primary prevention of infection. The secondary goal of prophylaxis is to diminish symptomatology and parasitemia in those infected long enough to allow medical attention to be sought. Generally prophylactic regimens include either a single drug or combination prophylaxis starting 1-2 weeks before travel to the malarious areas and continued for 4 weeks after departure from the areas. Drugs used for malaria prophylaxis are summarised in Table I[8-14]. For travel to areas where risk is generally low and seasonal or no risk of chloroquine resistant *P. falciparum* has been reported, once-weekly chloroquine is effective. Alternatively, when risk is very low, for example in urban areas, one may do without prophylaxis but use chloroquine as treatment when malaria occurs. In areas where low-risk or only low-level or focal CRPF has been reported, chloroquine alone or with the addition of proguanil can be used. Quinine, mefloquine or fansidar may be used as stand-by treatment. For travel to CRPF endemic areas which include Africa, South-East Asia especially Northern Thailand, Myanmar and Kampuchea, where risk of infection is high and multi-drug resistant *P. falciparum* has been reported, chemoprophylaxis is more difficult. Mefloquine and doxycycline have been advocated. If unavailable, chloroquine with proguanil may serve as an alternative with quinine or mefloquine as stand-by therapeutic drugs. Should symptoms develop, prompt medical attention is essential and can be life saving.

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Table I – Drugs used in malaria prophylaxis

Drugs	Usual dose per tablet/ capsule	Adult dose	Paediatric dose
Chloroquine	150mg (base) 100mg	300mg (base) once a week	5mg/kg base po once a week to maximum of 300mg
Proguanil	100mg	200mg once a day	<2yrs: 50mg/kg/day 2-6yrs: 100mg/day 7-10yrs: 150mg/day >10yrs: 200mg/day
Pyrimethamine/ Sulfadoxine (Fansidar)	25mg/ 500mg	1 tab. po once a week	2-11 month: 1/8 tab. 1-3yrs: 1/4 tab. 4-8yrs: 1/2 tab. 9-14yrs: 3/4 tab. >14yrs: 1 tab.
Mefloquine	250mg	1 tab. po once a week	15-19kg: 1/4 tab a week 20-30kg: 1/2 tab a week 31-45kg: 3/4 tab a week >45kg: adult dose
Doxycycline	100mg	100mg once a day	>8yrs: 2mg/kg oral daily up to adult dose
Pyrimethamine/ dapsone (maloprim)	12.5mg/ 100mg	1 tab. po once a week	5-10yrs: 1/2 tab. >10yrs: 1 tab.

Table II – Treatment of acute malaria infection

I) **All Malaria except CRPF:**
Tab Chloroquine 600mg (base) stat. followed by
Tab Chloroquine 300mg 8 hours later, followed by
Tab Chloroquine 300mg once a day for 2 days
Followed by primaquine 15mg once a day for 14 days
for *P. vivax* and *P. ovale* infection.

II) **CRPF:**

a) Mild infection (uncomplicated, parasite count <3%)
Tab Quinine 650mg tid for 7-10 days, or
Tab Mefloquine 1 gm stat.

b) Moderate-severe infection (parasite count >3%-5%):
i/v quinine load 7mg/kg over 30mins followed by
i/v quinine 10mg/kg (slow infusion over 4 hrs)
or i/v quinine load 20mg/kg over 4 hours
maintenance dose,
i/v quinine 10mg/kg over 4 hours to be given 8 hourly
monitor quantitative parasite count,
blood sugar level,
electrolyte/creatinine and
haemoglobin level.

convert to oral quinine when condition improves,
complete 7-10 days of therapy.

c) other modalities:
Tetracycline/doxycycline + quinine
Clindamycin + quinine
Qinghaosu / artesunate / artemether
Quinolone ?
Exchange transfusion ?

Treatment of acute malaria infection

When a *P. falciparum* infection has been identified, and unless the patient is able to provide a detailed history of the area of exposure which is non-CRPF endemic, it is safer to assume that the parasite is chloroquine-resistant as sensitivity tests are not readily available. Severe malaria is caused by *P. falciparum* in nearly all cases. It is a medical emergency. Children with falciparum infection are prone to develop hypoglycaemia, lactic acidosis, convulsions and severe anaemia. Pregnant women are particularly vulnerable to severe disease with increased mortality. Foetal loss is common and the mother is at high risk for hypoglycaemia and acute pulmonary oedema. A distinctive feature of *P. falciparum* infection is sequestration of infected red blood cells which produce an "artificially" low parasite count on the peripheral blood smear even in patients with severe infection[8]. Nonetheless, regular quantitative counts are essential to first determine the severity of infection in conjunction with the clinical features and later to monitor response to the therapy. This is particularly important in patients with severe infection who have parasite counts equal to or more than 5%. A poor response to treatment should arouse suspicion of a resistant strain. In such circumstances, additional anti-malaria drugs should be considered. Combined use of quinine and tetracycline had been advocated in parts of Thailand to treat multi-drug resistant *P. falciparum* infection[15]. Table II summarises the approach to the treatment of acute malaria infection[11-26]. Recent trials on the use of qinghaosu (artemisinin) and its derivatives, artemether and artesunate have been promising[16-20]. Artemether gave a rapid improvement in Gambian children with severe malaria[18]. Intravenous and intramuscular artisunate as well as artemisinin suppositories had been reported to give good results for the treatment of severe malaria in Vietnam[19,20]. Norfloxacin was the first fluoroquinolone to show a promising result in the treatment of uncomplicated falciparum malaria in India [21]. Unfortunately, results from several subsequent studies were disappointing[22,23]. Although clindamycin alone has been shown to be effective in some malaria endemic areas in the treatment of uncomplicated falciparum infections, it should be reserved for use as an additional drug to quinine in non-immune patients with multi-resistant *P. falciparum* infection[24]. Dexamethasone was reported to have adverse outcome in cerebral malaria and its use is contraindicated[25]. Exchange transfusion in heavily parasitised patients is controversial. Quinine was noted to induce insulin secretion that may precipitate hypoglycaemia in falciparum infection[26]. Regular monitoring of blood glucose levels is particularly important in children and pregnant women.

Adverse Reactions and Contraindications

The frequency and seriousness of side effects vary with the anti-malaria agents. Chloroquine or hydroxychloroquine rarely give rise to serious side effect when taken at prophylactic doses. Minor side effects such as gastrointestinal upset, headache, dizziness may occur and generally do not require drug discontinuation. Retinopathy has not been reported to be associated with weekly use of chloroquine in malaria prophylaxis. However, periodic ophthalmologic screening for persons using chloroquine for prolonged durations (ie more than 6 years of cumulative weekly prophylaxis) is recommended[9].

Many side effects have been reported from the use of fansidar. These range from mild cutaneous manifestations to death. The frequency varies from different centres and ethnic groups. It has been estimated that the incidence of fatal cutaneous reactions associated with the use of fansidar among American travellers ranges from 1/11,000 to 1/25,000 users[9]. If fansidar is used for prophylaxis, the traveller should be advised to stop immediately when cutaneous or mucocutaneous symptoms occur. Fansidar is contraindicated for persons with a history of sulpha drug allergy and infants under 2 months of age. The safety of fansidar during pregnancy has not been established and should, therefore, be avoided if possible.

Mefloquine is a relatively new antimalarial drug, and has

now been extensively used in CRPF areas. Adverse reactions are infrequent at prophylactic doses. However, as it has been associated with asymptomatic sinus bradycardia and a prolonged QT interval, it should not be given to those receiving beta-blockers, calcium antagonists, or drugs that may prolong or alter cardiac conduction. Other minor side effects include dizziness, disturbance of balance and occasionally convulsion in persons with preexisting central nervous system disorder[8,9].

Doxycycline is a tetracycline with a long half-life, hence it can be used once a day for malaria prophylaxis. It is advisable to begin 1-2 days before departure and to continue daily when remaining in the endemic areas till 4 weeks after returning from endemic areas. Travellers who use doxycycline should be aware of photosensitivity associated with its use[9]. Doxycycline or tetracycline should not be used in pregnancy in view of hepatotoxicity and in children less than 8 years of age to avoid abnormal bony development, discolouration and dysplasia of their teeth[8,9].

Primaquine is the only drug effective in eradicating the exoerythrocytic phase of *P. vivax* and *P. ovale* infection. Before using primaquine, G6PD deficiency should be excluded. It is contraindicated in pregnancy due to the unknown G6PD status of the foetus. To avoid possible foetal haemolysis, pregnant women can delay primaquine use until delivery. If *P. vivax* relapses occur, they may be safely treated with courses of chloroquine while awaiting delivery. Alternatively, the pregnant woman can receive chloroquine once a week until delivery[9].

Special attention

Pregnant women and new born infants should avoid malaria endemic areas. If unavoidable, the use of chloroquine and proguanil are relatively safe[8,9,11]. For infants less than 2 months old, sulphonamides are contraindicated owing to the immaturity of several liver enzyme systems. Nursing mothers should be told that the amount of drug secreted in breast milk is inadequate to protect their suckling infants and the potential toxicity of these medications to their infant is as yet undetermined[9,11].

There is no evidence to suggest that immunocompromised patients are at increased risk of malaria infection but they should avoid malaria endemic areas whenever possible[11].

Vaccination

Progress on malaria vaccines has been slow owing to stage and species specificity. A safe and effective malaria vaccine is not yet available. Emphasis has been on the production of a sporozoite vaccine, but it must completely neutralise every penetrating sporozoite as the escape of one sporozoite entering the liver is enough to give rise to clinical infection. Experimental vaccines against the blood stage of malaria have been effective in abolishing symptoms and preventing lethal complications from malaria infection. However, their use is still under study due to the multiple variable antigenic sites. A gametocyte vaccine aimed at the sexual stage of the life cycle would only protect the community but not the individual[27-30].

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