MALARIA ANTIMICROBIAL RESISTANCE - AN UPDATE FOR THE FAMILY PHYSICIAN IN SINGAPORE

Dr Farhad Fakhrudin Vasanwala

SFP2014; 40(1): 68-71

INTRODUCTION

Singapore remains vulnerable and receptive to the reintroduction of malaria despite being declared malaria free by the WHO since 1982.[1,2] Nonetheless, local outbreaks have taken place due to importation of patients/workers with malaria from their travels overseas.[3] In 2009, an outbreak in Sembawang and Mandai were detected from the clusters of Anopheles mosquitoes.[4]

Malarial drug resistance is now widespread among the world. Chloroquine prophylaxis is no longer sufficient for their travel to endemic malarial regions. As family physicians our role is to advise our patients on their need to take effective chemoprophylaxis for their travels overseas, and be vigilant for patients suffering from possible malaria especially those back from their travels. As anopheles mosquito is still indigenous in Singapore, we should consider doing a malaria workup for those patients presenting with fever of unknown origin, despite their lack of recent travel.

This paper gives a an update of the current

- local epidemiological data.
- the unique features of the various plasmodium species in Singapore.
- the current state of drug resistance against malaria drugs, how it affects the chemoprophylaxis and brief discussion on the prevention and management of patients with malaria.

LOCAL EPIDEMIOLOGICAL DATA

The Ministry of health statistics in 2013 showed that the predominant profiles of patients and malaria plasmodium species in Singapore are those[5]:

- Aged 15-54 years (80%).
- Singaporean residents, work permit/ employment pass holders (62%), tourists (15%) and those from overseas seeking medical treatment here (17%).
- Predominant forms of Malaria detected locally were Plasmodium vivax (75%) and P falciparum (18%). It is interesting to note that there was one patient with both Plasmodium vivax and P falciparum infection, hence concomitant infection with different plasmodium species is possible.

Most of the Singaporeans, work permit/ employment pass holders contracted malaria during their travels overseas for social visits and holidays in malaria endemic areas of South East Asia and the Indian subcontinent. Almost all of these patients did not take effective and or adhered to the regular chemoprophylaxis during their travel overseas.[5]

PLASMODIUM SPECIES IN SINGAPORE

Malaria Life Cycle

Figure 1 shows the malaria life cycle which is crucial in understanding the management of our patients for chemoprophylaxis and the treatment of malaria. It is important to remember that P. vivax and P. ovale have a dormant stage (hypnozoites) that can persist in the liver, and cause relapses by invading the bloodstream weeks or even years later.

The most malignant types of malaria are P falciparum and P knowlesi (a simian type of malaria that affects humans and have been found present in Singapore)[5] Unique to P falciparum is its ability to infect red blood cells (RBCs) of all ages resulting in parasitemia (>5% of RBCs infected). In contrast, P vivax and P ovale infect only young RBCs and thus cause a lower level of parasetemia (usually less than 2%).

Sequestration is a specific property of P falciparum, which results in the sequestration of the parasite in small postcapillary vessels, which contributes to the mental-status changes and coma observed exclusively in P falciparum infection. In addition, cytokines and a high burden of parasites contribute to end organ disease involving especially the central nervous system e.g. cerebral malaria, lungs e.g. pulmonary oedema or acute respiratory distress syndrome and kidneys e.g. nephrotic syndrome, renal failure.[6]

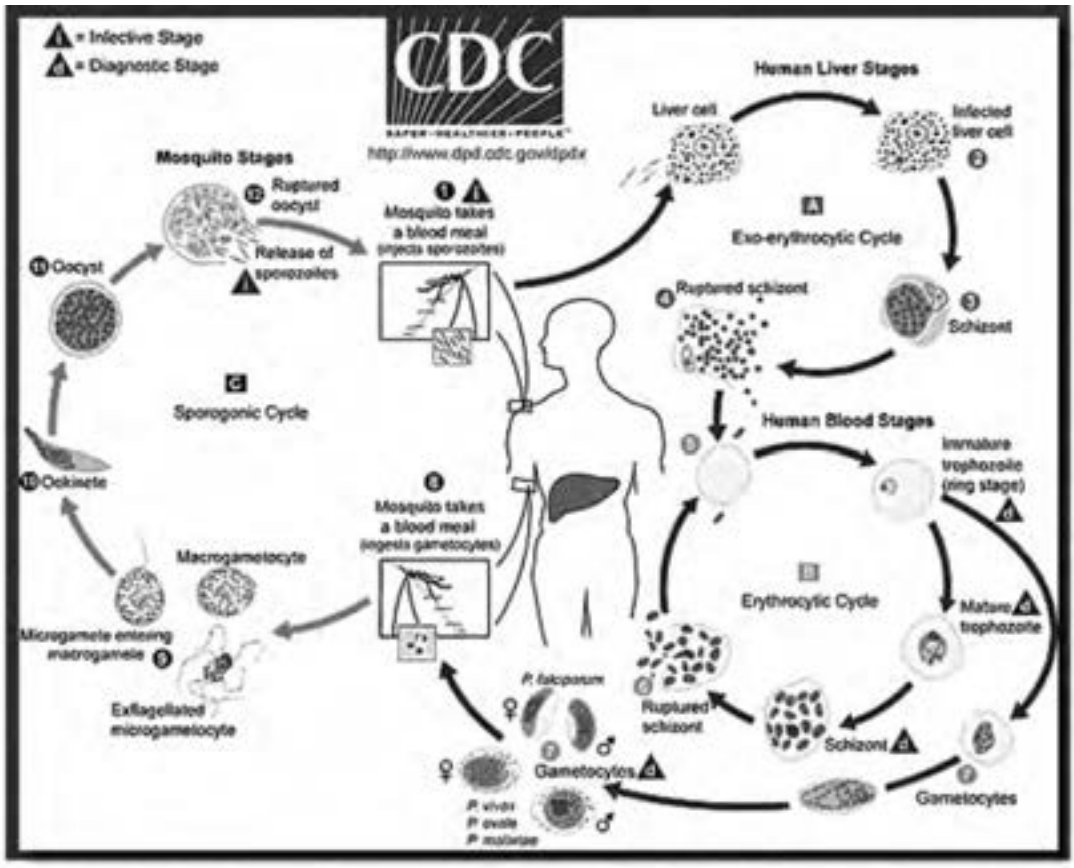
P knowlesi has a life-cycle of 24 hours and can give rise to daily fever spikes occurring 9–12 days after infection. Severe P. knowlesi malaria with organ failure may occur, and sporadic fatal outcomes have been described. P. knowlesi has no persistent liver forms and relapses do not occur.[7]

Clinical symptoms of malaria include some of the following:[9]

- Headache (noted in virtually all patients with malaria).
- Cough.
- Fatigue.
- Malaise.

FARHAD FAKHRUDIN VASANWALA, Consultant, Department of Internal Medicine, Singapore General Hospital

FIGURE 1. MALARIA LIFE CYCLE[8]



- Shaking chills.
- Arthralgia.
- Myalgia.
- Paroxysm of fever, shaking chills, and sweats (every 48 or 72 hours, depending on the species).

Less common symptoms include the following:
- Anorexia and lethargy.
- Nausea and vomiting.
- Diarrhoea.
- Jaundice.

Physical findings

Most patients with malaria have no specific physical findings, but splenomegaly may be present.

Severe malaria manifests as the following:

- Cerebral malaria.
- Severe anaemia.
- Respiratory abnormalities-include metabolic acidosis, pulmonary oedema or acute respiratory distress syndrome.
- Renal failure.

The possibility of falciparum malaria must be considered in all cases of unexplained fever starting at any time between seven days after the first possible exposure to malaria and three months (or, rarely, later) after the last possible exposure. Any individual who experiences a fever in this interval should immediately seek diagnosis and effective treatment, and inform medical personnel of the possible exposure to malaria infection. Falciparum malaria may be fatal if treatment is delayed beyond 24 hours after the onset of clinical symptoms[7].

Note that malaria can be devastating during pregnancy to the mother and the foetus. Maternal complications are thought to be mediated by pregnancy associated decreases in immune function, as well as by placental sequestration of the P falciparum parasites. Anaemia from malaria can be more severe in pregnant women. Fetal complications include premature birth, anaemia, low birth weight, and death. Malaria during the first trimester of pregnancy increases the risk of miscarriage.[10]

If the physician suspects that the patients has a possible malaria infection, multiple thick (for screening) and thin blood films (for speciation of the plasmodium) be done. Alternative tests that can be done are rapid diagnostic tests kits, polymerase chain reaction assay, nucleic acid sequence based amplification, and quantitative buffy coat.[9]

ANTIMALARIAL DRUG RESITANCE

There is a need for knowledge on antimalarial drug resistance not only locally but also globally in today's connected world of jet travel.

TABLE 1. ANTIMALARIAL DRUGS FOR CHEMOPROPHYLAXIS

Drug	Reasons that might make you consider using this drug	Reasons that might make you avoid using this drug
Atovaquone/ Proguanil (Malarone)	• Good for last-minute travellers because the drug is started one to two days before travelling to an area where malaria transmission occurs • Some people prefer to take a daily medicine • Good choice for shorter trips because you only have to take the medicine for seven days after travelling rather than four weeks • Very well tolerated medicine side effects uncommon • Pediatric tablets are available and may be more convenient	• Cannot be used by women who are pregnant or breastfeeding a child less than five kg • Cannot be taken by people with severe renal impairment • Tends to be more expensive than some of the other options (especially for trips of long duration) • Some people (including children) would rather not take a medicine everyday
Chloroquine	• Some people would rather take medicine weekly • Good choice for long trips because it is taken only weekly • Some people are already taking hydroxychloroquine chronically for rheumatologic conditions. In those instances, they may not have to take an additional medicine • Can be used in all trimesters of pregnancy	• Cannot be used in areas with chloroquine or mefloquine resistance • May exacerbate psoriasis • Some people would rather not take a weekly medication • For trips of short duration, some people would rather not take medication for four weeks after travel • Not a good choice for last-minute travellers because drug needs to be started one to two weeks prior to travel
Doxycycline	• Some people prefer to take a daily medicine • Good for last-minute travellers because the drug is started one to two days before traveling to an area where malaria transmission occurs • Tends to be the least expensive antimalarial • Some people are already taking doxycycline chronically for prevention of acne. In those instances, they do not have to take an additional medicine • Doxycycline also can prevent some additional infections (e.g., Rickettsiae and leptospirosis) and so it may be preferred by people planning to do lots of hiking, camping, and wading and swimming in fresh water	• Cannot be used by pregnant women and children <eight years old • Some people would rather not take a medicine every day • For trips of short duration, some people would rather not take medication for four weeks after travel • Women prone to getting vaginal yeast infections when taking antibiotics may prefer taking a different medicine • Persons planning on considerable sun exposure may want to avoid the increased risk of sun sensitivity • Some people are concerned about the potential of getting an upset stomach from doxycycline
Mefloquine (Lariam)	• Some people would rather take medicine weekly • Good choice for long trips because it is taken only weekly • Can be used during pregnancy	• Cannot be used in areas with mefloquine resistance • Cannot be used in patients with certain psychiatric conditions • Cannot be used in patients with a seizure disorder • Not recommended for persons with cardiac conduction abnormalities • Not a good choice for last-minute travellers because drug needs to be started at least two weeks prior to travel • Some people would rather not take a weekly medication • For trips of short duration, some people would rather not take medication for 4 weeks after travel
Primaquine	• It is the most effective medicine for preventing P. vivax and so it is a good choice for travel to places with > 90% P. vivax • Good choice for shorter trips because you only have to take the medicine for seven days after traveling rather than four weeks • Good for last-minute travellers because the drug is started one to two days before traveling to an area where malaria transmission occurs • Some people prefer to take a daily medicine	• Cannot be used in patients with glucose-6-phosphatase dehydrogenase (G6PD) deficiency • Cannot be used in patients who have not been tested for G6PD deficiency • There are costs and delays associated with getting a G6PD test done; however, it only has to be done once. Once a normal G6PD level is verified and documented, the test does not have to be repeated the next time primaquine is considered • Cannot be used by pregnant women • Cannot be used by women who are breastfeeding unless the infant has also been tested for G6PD deficiency • Some people (including children) would rather not take a medicine every day • Some people are concerned about the potential of getting an upset stomach from primaquine

Antimalarial drug selection for the traveller

The selection of drug has to be made with considerations of regions with malarial drug resistance. CDC in United States provides an up to date comprehensive website on the prophylaxis required.[11]

- Chloroquine sensitive P falciparum exists in Mexico, the Caribbean, Central America west and north of the Panama Canal and parts of North Africa, the Middle East.
- Chloroquine resistant P falciparum is widespread in endemic areas of Africa, Asia and Oceania.
- P falciparum strains resistant to chloroquine, mefloquine, sulphonamides, artemisinin are prevalent in the Cambodian Thai border, especially in the Greater Mekong Sub region and parts of China, Laos and Vietnam.[12]
- Chloroquine resistant P vivax is widespread in Indonesian Papua and Papua New Guinea.

Use of primaquine is appropriate for areas where there is substantial transmission of P vivax or P ovale (to treat the hypnozoites), even if the P falciparum is the predominant endemic species.

A prescription for the full supply of the medication should prescribed and filled prior to departure as the sale of counterfeit and poor quality antimalarials pose a significant problem in Asia and Africa which lead to drug resistance and inadequate treatment.[13]

Family physicians should also recommend their patient not to frequent places where the mosquito vector is known to be active. This mosquito vector bites mostly at dusk and at night. If they cannot avoid going to these places, it is advisable that their clothes completely cover the arms, legs and advise them to put on insect repellents. They should also use mosquito coils and repellents, and sleep under mosquito netting.[14]

When several different drugs are recommended for an area, the following table (Table 1) might help in the decision process.

General recommendations for pharmacologic treatment of the patient with malaria.[9]

Patient detected to have Malaria should be referred immediately to the hospital for treatment.

The general principles are:

- P falciparum malaria: Quinine-based therapy is with quinine or quinidine suphate plus doxycycline or clindamycin or pyrimethamine-sulfadoxine. Alternative therapies are artemether-lumefantrine, aovaquone-proguanil, or mefloquine.
- P falciparum malaria with known chloroquine susceptibility (only a few areas in Central America and the Middle East): Chloroquine.
- P vivax, P ovale malaria: Chloroquine plus primaquine.
- P malariae malaria: Chloroquine.
- P knowlesi malaria: Same recommendations as for P falciparum malaria.

CONCLUSIONS

Singapore's remains vulnerability to malaria is accentuated by its status as a trade and travel hub, high dependency on foreign workers from neighboring endemic countries, and increased regional travel to and from malarious areas.4 The family physician is the key pillar in advising our patients on appropriate chemoprophylaxis regularly based on up to date information available on line. As physicians we should remain vigilant and consider patients having possible malarial infection even if the patient has last travelled one year back.

REFERENCES

1. Lee YC, Tang CS, Ang LW, Han HK, James L, Goh KT: Epidemiological characteristics of imported and locally-acquired malaria in Singapore. Ann Acad Med Singapore 2009, 38:840-49.
2. Goh KT, 1983. Eradication of malaria from Singapore. Singapore Med J 25: 255-68.
3. Lim J, Han HK, Lim S, Ooi PL: An outbreak of vivax malaria in the off shore islands. Epidemiol News Bull 2006, 33:55-58
4. Ng, L. C., Lee, K. S., Tan, C. H., Ooi, P. L et al Entomologic and molecular investigation into Plasmodium vivax transmission in Singapore, 2009. Malar J, 9, 305.
5. Vector borne and zoonotic diseases in Singapore. URL: http://www.moh.gov.sg/content/moh_web/home/Publications/Reports/2013/Communicable_Diseases_Surveillance_in_Singapore_2012.html Accessed 2014 Oct 1.
6. Arguin, P.M., Keystone, J.S. Prevention of malaria infections in travellers. UpToDate, 2014. URL: http://www.uptodate.com/contents/prevention-of-malaria-infection-in-travelers). Accessed 2014 Oct 1.
7. International travel and health, Malaria. URL: http://www.who.int/ith/diseases/malaria/en/ Accessed 2014 Oct 1.
Malaria Life Cycle. URL: http://www.cdc.gov/malaria/about/biology/ Accessed 1/10/2014
8. Jorge, E.V.P., Bronze, M.S. Malaria , Medscape. URL: http://emedicine.medscape.com/article/221134-overview. Accessed 2014 Oct 1.
9. McGready, R., Lee, S. J., Wiladphaingern, J., Ashley, E.A., et al. Adverse effects of falciparum and vivax malaria and the safety of antimalarial treatment in early pregnancy: a population-based study. The Lancet infectious diseases, 2010 12(5), 388-396.
10. CDC Malaria information and prophylaxis by country, resistance. URL: http://www.cdc.gov/malaria/travelers/country_table/a.html Accessed 2014 Oct 1.
11. Wongsrichanalai, C., & Sibley, C. H. (2013). Fighting drug-resistant Plasmodium falciparum: the challenge of artemisinin resistance. Clinical Microbiology and Infection, 19(10), 908-916.
12. Nayyar, G. M., Breman, J. G., Newton, P. N., & Herrington, J. Poor-quality antimalarial drugs in Southeast Asia and sub-Saharan Africa. The Lancet infectious diseases, 2012, 12(6), 488-96.
13. A new case of suspected of local malarial transmission at Jurong Island. URL: http://www.moh.gov.sg/content/moh_web/home/pressRoom/pressRoomItemRelease/2009/a_new_case_of_suspected_local_malaria_transmission_in_Jurong_island.html. Accessed 2014 Oct 1.
14. Choosing a Drug to Prevent Malaria. URL: http://www.cdc.gov/malaria/travelers/drugs.html Accessed 2014 Oct 1.