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Expert Opinion Case 2011-3

A 24 year-old Swiss traveler is departing in 3 weeks for prolonged travel in Asia. He is first flying to Hong Kong, next traveling throughout Thailand for two weeks, and will complete his trip with a one-month stay in India. His itinerary is very flexible in India, and he plans to travel to various cities and villages in the northern and southern parts of the country. He will be leaving next December and returning sometime in February.

How would you advise this traveler concerning his risk of malaria?

Learning Objectives

1. Describe generally the epidemiology of malaria in Hong Kong, Thailand and India.

Hong Kong, the first destination, has been free of endemic malaria since 1969, and there is thus no requirement for antimalarials for this part of the itinerary. However, malaria is present in some areas of southern China, and the travel health advisor might consider mentioning this, in the event the traveler amends his itinerary once in Hong Kong.

Not atypically for long term travelers, the given itinerary lacks detail: specifically this 'adventure traveler' is unlikely to be able to give an exact in-country itinerary for Thailand and India; the very nature of long term travel means it can be subject to itinerary change. Thus, even when travelers provide an apparently fixed itinerary, clinicians might consider building provision for unforeseen itinerary change into their recommendations.

Malaria in Thailand is confined to rural border regions and is present year round, with *P. falciparum* resistant to both chloroquine and mefloquine, and showing decreased sensitivity to quinine, present in the Thai-Burma border region. The incidence of malaria in travelers who have visited Thailand is <1 per 100,000 visitors.(1) This incidence may not give an entirely accurate picture of the risk faced by our traveler however, as large parts of Thailand are malaria free and many travelers will not be exposed at all.

The incidence of *falciparum* malaria in travelers to India from Western Europe is approximately 2 cases per 100 000 travelers.(2) Chloroquine resistant malaria is present through most of India below 2000m altitude. Higher risk states are identified as Chhattisgarh, Orissa, Jharkhand, and West Bengal, and the Indian states east of Bangladesh. Transmission may occur throughout the year, with seasonality patterns varying by region. Mefloquine resistance has been reported from remote areas. It is likely the true burden of malaria in India is underreported. *P. vivax* accounts for approximately 80% of malaria cases in travelers from India, and the risk of contracting this form of malaria is likely higher in India than in Thailand; current practice does not consider specific chemoprophylaxis against *P. vivax* necessary. The practitioner should bear in mind that chemoprophylaxis against *P. falciparum* will not protect against the later emergence of *P. vivax*.

2. Discuss risk/benefit calculation when considering malaria prophylaxis.

With regard to chemoprophylaxis of malaria, the basic risk/benefit calculation usually compares the risk of a serious adverse reaction to the prescribed antimalarial with the risk of contracting *falciparum* malaria. Simplistically, the risk of developing malaria should exceed the risk of experiencing a serious adverse drug reaction. However, as chemoprophylaxis is prescribed for generally asymptomatic individuals (and increasingly, those with stable coincidental illness), only a very low risk of serious adverse events will be acceptable.

Medication risk obviously varies with the antimalarial prescribed: the lower incidences generally being seen with atovaquone-proguanil and doxycycline, and mefloquine being less well tolerated, although reported incidences vary.(3)

The real difficulty with this type of risk/benefit calculation is in deciding what the acceptable level of medication risk really is, and what the real malaria risk is; although there is no shortage of sources offering advice on malaria risk, the true malaria risk facing a traveler will in most cases remain unknown.(4) Ultimately the decision to

prescribe prophylaxis will be a clinical one, and vary by practitioner, national and regional approach, and the views of the individual traveler. Regardless of whether chemoprophylaxis is prescribed, the traveler should be counseled on personal protection measures against mosquito bites.

The risk/benefit comparison for the treatment of malaria in contradistinction is much easier: left untreated, falciparum malaria is a progressive and fatal disease in the non-immune, and disease in travelers may be rapidly fatal.

3. Describe an approach to stand-by-therapy.

Although the current recommendations of the World Health Organization and the United States Centers for Disease Control are that travelers should be prescribed chemoprophylaxis where risk of falciparum malaria exists, some authorities have questioned this approach and begun to recommend the use of Stand-by Emergency Treatment (SBET).

Unfortunately, the strategies currently employed to protect travelers against malaria can never be 100% effective: travelers' compliance with recommendations remains problematic, doses may be missed and premature discontinuation of prophylaxis may occur, at times on the basis of real or imagined side effects. Occasionally, no obvious reason for prophylaxis failure can be established.⁴

The great majority of travelers from industrialized countries fall into the category of 'non-immune', for whom malaria may be rapidly progressive and fatal; for such travelers, falciparum malaria should be regarded as a medical emergency. Thus, prompt diagnosis and treatment are essential and can be lifesaving.

Travelers who develop malaria symptoms while abroad may experience significant difficulties in accessing competent medical care, and in accessing reliably efficacious medication: the quality of medication while abroad cannot always be guaranteed, with counterfeit medication circulating in many parts of the malarious world. Unfortunately, counterfeit medication may be very difficult to distinguish from genuine efficacious medication. For these reasons, travelers may at times be prescribed stand by emergency treatment (SBET), to self medicate with should they develop symptoms of malaria in circumstances where quality medical care and medication are unavailable. Provision of SBET before departure should also protect against unwitting acquisition of counterfeit medication while abroad.

In recent years the advent of newer, better tolerated, drugs for the treatment of malaria has occasioned a rethink of the use of SBET, especially for travelers to low risk destinations. There can be no hard and fast rule or substitute for clinical judgment on which travelers might be suitable candidates for the provision of SBET, but a number of factors should be weighed when considering this approach; table I provided below might assist with this determination.(5)

It is important to emphasize that the use of SBET by travelers does not absolve them of the need to seek competent medical advice. SBET is intended only as a stopgap measure to prevent severe disease and loss of life. In essence, SBET is intended to 'buy time' for the traveler, so he can get himself to competent medical care.

A further difficulty is that self-diagnosis of malaria may be unreliable. Rapid tests for the diagnosis of malaria are not 100% sensitive and may give false negative results, especially in inexperienced hands. Failure to self medicate in the event of a false negative test may be a fatal decision. Self diagnosis therefore ultimately will rest upon the traveler recognizing symptoms compatible with malaria. Travelers will therefore need to be educated on the symptoms of early malaria, and when SBET self administration might be indicated.

A false positive result, while disruptive to travel, is a less serious problem, as most stand by emergency treatment (SBET) likely to be provided has a good tolerability profile. This touches upon the question of potential harm to the traveler from the use of SBET in the absence of malaria. Again, the antimalarials usually selected for SBET are well tolerated in the acute setting, but this factor will need to be included in the prescriber's risk/benefit assessment. A possibly reassuring statistic is that only 0.5% of Swiss travelers prescribed SBET actually used the medication.(6)

Table I. Factors prescribers may wish to consider when contemplating SBET prescription:

PRESCRIBER TO CONSIDER	ACTION REQUIRED
Length of stay in risk area	<ul style="list-style-type: none"> ESBM not required if <7 days without access to competent care
Traveler's understanding of malaria's symptoms	<ul style="list-style-type: none"> Educate the traveler on malaria symptoms, especially fever Advise avoidance of delay in taking ESBM if fever appears Advise need to still urgently seek competent care
How likely is compliance	<ul style="list-style-type: none"> Exercise clinical judgment
Adverse drug effects are more likely with treatment than prophylaxis doses	<ul style="list-style-type: none"> Advise traveler of possible adverse drug effects
Simplicity of ESBM treatment regimen	<ul style="list-style-type: none"> Select ESBM with a simple dosing regimen to facilitate compliance

Malaria strain sensitivity at destination(s)	<ul style="list-style-type: none"> • Select ESBM likely to be effective against strains in risk areas
Drug storage conditions	<ul style="list-style-type: none"> • Advise traveler on appropriate carriage and storage • Retain in original packaging
Interactions with traveler's own medications	<ul style="list-style-type: none"> • Take detailed medical and medication history and avoid antimalarials with interaction potential (commonly QTc interval prolongation, epilepsy exacerbation)

Drugs Recommended for SBET

The agents most suitable for SBET are atovaquone-proguanil and artemether-lumefantrine, as they are well tolerated in the acute situation (Table 2); use of either agent for SBET may be off-label in some jurisdictions. Atovaquone-proguanil should be avoided for SBET if the traveller has been taking it for chemoprophylaxis.

Table 2. Drugs most commonly recommended for SBET

EMERGENCY STANDBY TREATMENT	ADULT DOSING REGIMEN
Artemether-lumefantrine	4 tabs per dose (hours 0, 8, 24, 36, 48, 60) with food
Atovaquone-proguanil	4 tabs once daily for 3 days with food

Conclusion

Given the low risk of acquiring *P. falciparum* at the intended destinations, this traveler could be considered for SBET. An alternative approach might be to confine SBET to the Thai portion of the itinerary and to consider chemoprophylaxis if higher risk states in India were to be visited. This approach is however complex and might lead to a compliance problem. If the practitioner believed the traveler might be exposed to a high

risk in Thailand, chemoprophylaxis with atovaquone-proguanil might be considered, as course length is shorter than with other agents. The ultimate decision on whether to recommend SBET for all or part of this itinerary would need to be based upon a clinical assessment that would include a frank discussion with the traveler of the risks and benefits of this approach for his stated and possible itineraries.

Reference List

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