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Malaria in the Traveller: How to Manage Before Departure and Evaluate Upon Return

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Abstract

Malaria is the clinical syndrome when a patient experiences symptoms in response to infection with one of several strains of the Plasmodium parasite. This manuscript is intended for healthcare providers to become familiar with some of the basics of care of the patient who is travelling to or returning from an area with ongoing malaria transmission. The specific focus of is on patients from non-endemic areas who plan on travel for a finite period to an area where malaria is endemic. Emphasis will be on placed on prevention and diagnosis. Risk factors for malaria acquisition will be discussed. We will have an evidence-based discussion of personal protective equipment, choice of chemoprophylactic agent, and pre-departure counseling that includes a discussion of malaria in the immunosuppressed patient. We will also review when to suspect malaria in a patient returning from an endemic area and the importance of rapid diagnostic tests in the diagnostic investigations. Finally, we will discuss how malaria is a sepsis syndrome that can progress quickly in populations with no pre-existing immunity.

Key terms

Malaria; Prevention; Chemoprophylaxis; Plasmodium; Fever in returning traveler

Overview

This manuscript will familiarize healthcare providers with the prevention, diagnosis, and treatment of malaria, with specific focus on patients from non-endemic areas who plan to travel for a limited time to an area with risk of malaria transmission.

Providers must understand malaria, because it is a disease estimated to kill nearly 600,000 people per year worldwide. Despite public health interventions that have reduced the global

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burden of morbidity and mortality, it remains highly prevalent throughout much of the world. For the general practitioner, it is important to recognize the clinical manifestations of malaria because it is the most common cause of fever in returning travelers [1], and one of the few conditions that can kill patients rapidly if mismanaged. In 2012, roughly 2,000 cases were seen in the United States, including six preventable deaths [2]. After reading this chapter, we hope that the reader will be able to prevent such needless loss of life.

Malaria

Malaria is an infection caused by any of five species of the *Plasmodium* parasite: *P.falciparum*, *P.vivax*, *P.ovale*, *P.malariae*, and *P.knowlesi* (Figure 1) These single-celled eukaryotic organisms are transmitted to humans by the bite of an *Anopheles* mosquito. Within minutes of the bite, parasites enter the liver, where they develop and multiply asymptotically. After 10–14 days, parasites leave the liver and enter the bloodstream, rapidly invading erythrocytes to feed on hemoglobin, multiply, and after 2–3 days erupt from the diseased cell to invade new erythrocytes. It is this erythrocytic phase of *Plasmodium*'s life cycle that is responsible for clinical illness.

In the case of *P.vivax* and *P.ovale*, some parasites may enter a “dormant” phase in the liver, which may reactivate months after initial reinfection. These “hypnozoites” require special treatment.

The plasmodium life cycle is completed when sexual forms of the parasites (“gametocytes”) are ingested by another *Anopheles* mosquito, allowing them to mate and develop within the insect.

Prevention: 4 Steps to Success

No vaccine for malaria prevention currently exists for travelers; exciting developments have taken place in the last decade, demonstrating at least partial protection of a live-attenuated vaccine when administered to children living in highly endemic areas. However, this vaccine is not approved or available for other patient groups. Thus, healthcare providers should be adept at a multi-pronged prevention strategy: Determine the malaria risk; counsel on mosquito avoidance techniques; prescribe chemoprophylaxis; and educate on warning signs of malaria.

Step 1: Determine whether the patient is at risk of malaria

1A: Geographic Risk Assessment—There are a number of publicly available resources that can assist in determining whether travel to a particular area is associated with the risk of developing malaria. Foremost is the CDC website (<http://www.cdc.gov/malaria>). There are also proprietary databases such as the travax website (<http://www.travax.com>) provide information regarding the current rate of malaria in a particular locale. In general, malaria is not endemic in areas above 3300 meters (10,800 feet). Nevertheless, because malaria can be quite fulminant in non-semi-immune populations, providers should err on the side of offering both advice and chemotherapy if the risk cannot be adequately described. In general, all patients travelling to sub-saharan Africa are at risk, unless their journey is

exclusively to highlands such as Mt Kilimanjaro; in fact, the bulk of imported cases in the USA originate in Africa.[4]

Further complicating travel advice, acquisition of malaria in and around airports is a well-described phenomenon [5]. However, travelers who will merely change planes or lay over in an airport in malarious regions are generally felt to be at very low risk of infection.

The risk of malaria may rise and fall in a given region based on the season of travel, with highest risk following sustained rains that fill pools with water where mosquitoes breed. However, in most endemic regions, some risk will persist year-round, and the time of travel during “the dry season” does not preclude the need for prevention measures.

On the other hand, real progress has been achieved in certain areas, where the risk of malaria is now negligible compared with years gone by. Whether this has happened due to mosquito control programs or climate change—or both—will vary from case to case. Regardless, it is worth consulting an up-to-date resource if you are not very familiar with a particular itinerary, because malaria prophylaxis may no longer be required, and vice-versa.

1B: Host Risk Assessment—Malaria can happen to any patient, even if they hail from an endemic area or have had malaria before, because the semi-immune state wanes within months after exposure ceases. But, some patients seem to be exceptionally susceptible to malaria, and deserve special counseling. The strongest association is with HIV/AIDS, where frequency of malaria episodes rises as CD4 counts fall.[11] Patients who have HIV should be advised that they are at higher risk of malaria acquisition, although if they have a high CD4 count and good virologic control the magnitude of the risk is unknown and probably similar to that in patients without HIV. Of note, trimethoprim-sulfamethoxazole is NOT adequate malaria prophylaxis in patients travelling to Africa (see below).

Asplenia is another well-described risk factor for development of malaria. Patients from an endemic area in Malawi who are asplenic from trauma have been demonstrated to have increased risks of clinical malaria and have higher parasite densities with *Plasmodium falciparum* than age-matched controls [12]. Of note, this was from a population with pre-existing immunity to malaria. Therefore, the risk of severe malaria and the clinical course of infection in a naive individual is unknown. Laboratory investigations have demonstrated that both congenitally asplenic and surgically splenectomized mice have a uniformly fatal outcome with malaria infection[13]. Part of any routine counseling prior to departure to a malaria endemic area should include whether the patient is either anatomically or functionally asplenic.

We also encourage evaluation of other immunosuppression. We would especially include exposure to medications that deplete or affect the B-cell compartment, such as anti-CD20 antibodies (e.g. rituximab). Babesiosis, an analogous intraerythrocytic parasitic disease, is substantially worsened when monoclonal antibodies are given against CD20 (rituximab). In animal studies, b-cell depletion leads to death from infection and repletion of immune serum has been used therapeutically in malaria infections. Therefore, it is reasonable to assume that any patient with an autoimmune disease on immunomodulatory therapy that affects the B-

cell compartment (or CD4+ t-cell subset) would be at increased risk for both development of clinical malaria and worse disease outcomes.

Step 2: Counsel on mosquito avoidance techniques

Malaria is a vector-borne illness acquired during the bite of a female *Anopheles* mosquito. An important feature of this mosquito vector is night-time feeding behavior. This stereotypical behavior makes bed nets an important part of prevention of the disease. Although the efficacy of bed nets in non-endemic populations is unknown, meta-analysis of studies in endemic areas bed nets have demonstrated reduction in the episodes of clinical malaria, the community burden of Plasmodium parasite, and mortality associated with malaria [6]. Since there are no known risks associated with the use of insecticide treated bed nets, usage should be encouraged in any prospective traveler to a malaria endemic area.

Other basic counseling should stress the need for general protection against insect bites. This has additive benefit, because preventative solutions that reduce mosquito bites also protect against most insect-borne disease (e.g. ones not prevented by bednets or malaria chemoprophylaxis such as dengue and rickettsial disease). Long sleeves and pants should be encouraged (which also affords protection from sunburn). If possible, permethrin impregnation should also be used, because this has been demonstrated to both reduce insect bites through clothing by 99% and also insect bites of unprotected persons in the nearby area by 94% [7]. All of the bites in subjects wearing permethrin-coated clothes were in areas of uncovered skin. Therefore, usage of oil-based repellents such as picaridin or DEET should be encouraged in conjunction with protective clothing. DEET concentrations should be at least 24%, as lower concentrations are less reliably effective [8]. Protective measures are discussed in greater detail in Chapter 3.

Step 3: Prescribe Chemoprophylaxis

Preventative medications (chemoprophylaxis) should be offered to any person travelling to an area where malaria is prevalent (Table 1). When taken properly, it is highly effective in preventing malaria acquisition. For example, in one Dutch study, none of 653 patients who took appropriate prophylaxis was diagnosed with clinical malaria.[14] It should be noted, however, that the degree of protection probably depends on exposure. In studies of US military personnel in Somalia, breakthrough infections were described in patients with documented therapeutic levels of both doxycycline and mefloquine [15]. In the Somali experience, guard duty near the Jubba river, where bite intensity was high, was identified as a strong risk factor.

Non-compliance is a major obstacle to effective chemoprophylaxis, and has been repeatedly identified as a risk factor for development of clinical malaria. Typically, chemoprophylaxis is intended for persons with a time-limited exposure to malaria, when sustainable compliance is realistic. The early parasite stages are resistant to medication effect, so all agents must be continued for some period of time following exposure, from 1–4 weeks depending on the drug, which further complicates adherence.

The role of long-term chemoprophylaxis for persons living in an endemic area needs to be discussed on an individual basis. Studies of compliance in long-term expatriates have demonstrated that willingness to take long-term prophylaxis drops dramatically (to less than 40% of the population) beyond roughly three months of [16].

There are several options for chemoprophylaxis, and no head-to-head superiority trials exist. All FDA-approved regimens have been highly effective—when patients are compliant—and very well tolerated. [14] Therefore, the choice of drug can be customized on the basis of patient preference, side effect profile, and cost. In large surveys of European travelers, atovaquone-proguanil is the most frequently prescribed agent for short-term travelers (defined as less than three months) whereas mefloquine is generally recommended for long term travel.

Geographic Considerations: New World versus Old World—Leading options for chemoprophylaxis include doxycycline, mefloquine, and atovaquone-proguanil. Although antifolate drugs (trimethoprim-sulfamethoxazole, sulfadoxine-pyrimethamine) are active against malaria, the parasite has developed resistance to these agents in sub-Saharan Africa, and they have failed in clinical trials of prophylaxis in pregnant women.

Chloroquine—Although previously a mainstay of malaria treatment, this agent cannot be used outside of very limited situations. At this time, the only areas with reliably susceptible *Plasmodium* parasites are in Latin America west of the Panama Canal (the Darien region has well described chloroquine resistant strains) and the Caribbean. Long-term use is associated with retinal toxicity and the agent is contraindicated in patients with a history of psoriasis or epilepsy. In general, it is well tolerated, as evidenced by the safe long term use of its derivative (hydroxychloroquine) in patients with SLE. A long half life allows for once-weekly dosing. It is safe in pregnancy.

Advantages: Safe, well tolerated, usually affordable

Drawbacks: Worldwide Resistance Outside Caribbean.

Target population: Potential travelers to Caribbean (e.g. Haiti).

Typical adult dose: 500mg salt (300mg base) PO weekly, starting 2 weeks pre-exposure and continuing for 4 weeks post-exposure.

Mefloquine—Mefloquine is active against chloroquine-resistant strains and has a prolonged half-life that allows for once weekly dosing, and may mitigate the consequences of a slightly delayed dose. This makes it an attractive agent for persons who are going to be in malarious areas for a prolonged period of time. In studies of 369 US military personnel deployed to Somalia, mefloquine was actually better tolerated than doxycycline, with skin photosensitivity and gastrointestinal symptoms occurring in 20–30% of patients taking doxycycline versus 5–10% of patients taking mefloquine. No differences were observed in the rates of neuropsychiatric effects.

There is some controversy with respect to the neuropsychiatric effects of mefloquine. There are well-described adverse events, including severe neuropsychiatric incidents, and the

medication carries a warning label for patients with a history of psychiatric disorder. In general, the rate of neuropsychiatric problems is higher in women than with comparator drugs. The major symptoms were headache and sleep disturbances [14]. Our opinion is that the risk of neuropsychiatric effects is in general overstated, and that the rate of adverse reactions is quite low in both clinical practice and epidemiologic studies. Still, the risks and benefits should be discussed with the prospective patient. Special caution should be applied to situations whereby a patient cannot seek medical attention or would be in a remote or isolated situation.

Mefloquine is metabolized in the liver by cytochrome P450 3A4. This leads to many potential drug interactions, which should be considered prior to prescription of mefloquine. It is safe in pregnancy.

Advantages: Once weekly dosing makes ideal long term regimen, little resistance.

Drawbacks: Minority of patients experience neuropsychiatric effects; many drug interactions (Cyp3A4).

Target: Peace Corps volunteers in remote areas; long-term volunteers or employees.

Typical adult dose: 250 mg salt (228 mg base) PO weekly, starting 2–3 weeks pre-exposure, and continuing 4 weeks post-exposure.

Atovaquone-Proguanil—Atovaquone-proguanil is a co-formulated drug that acts synergistically against the malaria parasite and can be used for either treatment or prophylaxis. Atovaquone itself was found to be inadequate as monotherapy for treatment of established malaria infections and rapidly induces resistance, so we would not recommend use as monotherapy.

One particular advantage of atovaquone-proguanil is that it has activity against the liver stage. Therefore, the patient does not have to take the medication for as long as other prophylactic options upon return from a malarious area. The FDA package insert recommends taking the medication for one week upon return from a malarious area, and we support this practice. In Israel, however, a frequent recommendation is to cease taking the medication one day after return, based on passive surveillance there which detected no failures [17]. It is probably safe during gestation, but conclusive trials are lacking, thus its official status: contraindicated in pregnancy.

Advantages: Effective, well tolerated. Only need to take for short course upon return.

Disadvantages: Expensive.

Target: Short term exposure to malarious area.

Typical adult dose: 250 mg atovaquone + 100 mg proguanil PO daily, starting 2 days pre-exposure and continuing for 7 days post-exposure.

Doxycycline—Doxycycline can be utilized as monotherapy for prophylaxis of malaria, but not for treatment. Like all malaria chemoprophylaxis agents, it is in general well tolerated. There are two specific risks that we would highlight. The most common risk is esophageal

irritation. In general, this is the most common side effect but can be mitigated with precautionary advice. In a population of Dutch patients, no esophageal irritation was determined. Patients were counseled to take the pill with a glass of water after food and not to take the pill at least one hour prior to lying supine [14]. Because this antibiotic is effective against leptospirosis and rickettsial infections, it may be advantageous for patients in whom there is a high likelihood of exposure to fresh water or tick bites. It is contraindicated in pregnancy.

Advantages: Effective, well tolerated. Has activity against other potential pathogens including leptospirosis, rickettsia.

Disadvantages: Esophageal irritation/ulceration. Skin photosensitivity. Price varies unpredictably.

Target: Longer term exposure in patients likely to use sun protection and/or be exposed to other zoonotic pathogens (e.g. safari).

Typical adult dose: 100mg PO daily starting 2 days pre-exposure and continuing 4 weeks post-exposure.

Step 4: Educate on warning signs of malaria

For travelers going to an area where malaria is endemic, pre-departure counseling is an important element of malaria prevention. Advice has been shown to reduce the risk of both insect bites and malaria acquisition [3]. Most patients have heard of malaria, but have little understanding of what causes it, how it presents, or what the consequences may be. This can lead to both poor prevention compliance and delayed presentation to medical attention if clinical malaria develops—which can have life-threatening consequences. Patients who are returning to an area from which they immigrated are also at risk, because naturally acquired immunity wanes after leaving an endemic area. They should be offered advice and chemoprophylaxis the same as persons who have never been to an endemic area. In fact, the majority of patients diagnosed with malaria in 2012 the United States (66%) were returning from visiting friends and relatives, with over 90% returning from sub-Saharan Africa [2].

All patients should be referred to www.CDC.gov/malaria, which has excellent teaching materials. They should also be told these fundamental facts:

- Careful prevention techniques (bite avoidance, chemoprophylaxis) are excellent, but not perfect.
- Fever may be malaria, up to a year after coming home from an endemic area.
- Malaria can turn dangerous very quickly, and early diagnosis and treatment can save your life. Any fever should trigger a call or visit to a medical doctor for prompt assessment, up to a year after returning. Tell your health care provider that you were exposed to malaria.
- Even if you have lived in an endemic area for a long time, and even if you have had malaria before, you can get it again, and it can be very serious every time.

Clinical Presentation: Always Suspect Malaria in an Ill returning Traveler

Take home points

- flu-like symptoms are most common presentation
- clinical presentation of malaria is non-specific
- cyclical fevers are NOT characteristic of malaria
- diarrhea and abdominal pain are common
- malaria may co-present with other sources of fever

Malaria should be suspected in any patient with a febrile syndrome after returning from a malarious area. The typical syndrome described for acute uncomplicated malaria is described as an influenza-like illness, with fever, myalgias, and headaches. An underappreciated element of the syndrome is gastrointestinal illness. The pathophysiologic explanation for why patients who are immunologically naive experience abdominal pain and diarrhea is unclear, and this presentation differs from patients who experience malaria in an endemic area. But, the bottom line is that acute malaria often presents with diarrhea.

The classic “tertian” (every 48 hours) or “quartian” (every 72 hours) fever can still be found in many textbooks, but this pattern is rare among travelers, because it generally takes some time for the parasites to synchronize their life cycles. Clinicians should not consider the fever pattern in evaluating patients for malaria, and have an extremely low threshold for further diagnostic testing. Malaria is a well-described cause of sepsis, and delays in treatment have been implicated in poor outcomes [1].

Because there is a lag between the initial bite by an infected mosquito to progression and amplification in the liver stages of the parasite’s life cycle, and eventual the development of symptomatic blood-stage infection, patients should be counseled (and providers should be aware) that clinical malaria can develop up to one year after return from a malaria endemic area. For the majority of patients, however, the incubation period is on the order of 7–14 days. One hospital reported that the mean time of patients return from an endemic area and presentation to the hospital was 9.5 days (3–14) [9]

There are major differences in the life cycle between the four species of *Plasmodium* that infect humans and this difference should be explained to patients. *Plasmodium falciparum*, the most common cause of malaria in travelers, is not associated with a residual liver stage. Therefore, if a patient is effectively treated and recovers, the chance of late relapse is extremely low. This is not the case for *Plasmodium vivax* and *Plasmodium ovale*, which have residual liver stages called “hypnozoites.” Therefore, even with adequate acute treatment a patient can experience relapse months or years later. Experiences with military veterans returning from the Korea war documented relapses up to thirty years after return (with no subsequent exposure). More recent studies of Australian military personnel who were treated for malaria with *Plasmodium vivax* infections during deployment to East Timor, relapses happened on the order of nine months after a clinical infection (median 180 days).[10] The longest documented relapse was 777 days.

Finally, malaria should remain on the differential diagnosis and ruled out definitively even if an alternative source of fever is detected in a returning traveller. Respiratory infections, GI infections, or urinary infections may co-exist with malaria, and should not distract the provider from continuing to rule out malaria, especially when they fail to respond to treatment.

Diagnosis

Take home points

- thick and thin smears are useful for prognosis but are operator dependent
- rapid diagnostic tests can be quickly used to distinguish babesia from malaria

Smear—Despite being developed over 100 years ago by Ronald Ross, microscopic evaluation of peripheral blood smear remains the only technique for which qualitative, quantitative, and prognostic factors are assessed in one inexpensive test. The reagents for preparing a peripheral smear should be available at most large healthcare facilities: Wright-Giemsa stain, slides, and a microscope. Unfortunately, the human element of technologists and clinicians familiar with malaria varies considerably between institutions. In general, areas of lower prevalence and less experience with malaria will have less reliable smear microscopic evaluation.

Smears are always ordered in pairs: thick and thin. The thick smear is roughly 30 times as sensitive as the thin smear, because much more blood is used on each slide; however, thick smears do not provide reliable information on the species or burden of infection. Thin smears show the parasites clearly, and allow a skillful operator to identify the species and to count the parasitemia at the same time.

A single negative pair of smears does not exclude the diagnosis of malaria. This is because of the episodic nature of parasitemia, in which detectable parasites may appear on the smear at one point in the day, then disappear hours later. Thus, ideally, smears should be repeated every 8 hours for 48 hours to achieve an optimal negative predictive value. The Thai experience is illustrative, as the clinical laboratories in Thailand are thought to have some of the highest quality microscopists. When experienced microscopists were asked to evaluate smears, the diagnostic yield had a false negative rate of roughly 10–15% when compared to more stringent research analysis conducted as part of the Armed Forces Research Institute of Medical Science (AFRIMS) [18]. Furthermore, clinicians should be aware that false positive results are also possible (in the Thai experience, these were more common than false negatives, at roughly 25%). The rate of both false positives and false negatives was strongly influenced by the density of parasites in the blood, as lower densities of parasites were strongly associated with both false positive and false negative results. Caution should be advised as platelets, red blood cell fragments, and staining artifacts are all reported to be confused with malaria parasites. Malaria coinfection can also occur, so even with a firm diagnosis of malaria clinicians should seek to exclude alternative explanations for febrile syndromes if the patient does not respond to anti-malarial therapies.

Rapid Diagnostic Tests—Rapid diagnostics are based upon the same immunochromatographic technology as standard home pregnancy test (Figure 2). Most rapid diagnostics use blood from finger pricks (although venous blood will work). In general, rapid diagnostics offer comparable sensitivity to smear microscopy with much less interobserver variability. There are a variety of different brands, but in general the target of the bands is a malarial antigen expressed in blood stage infection. Some brands differentiate between the various malaria species, whereas others do not. It is important for the clinician to be aware of the difference in brands. Health care providers in non-endemic areas often underutilize these valuable tests, although the use of rapid diagnostics has been demonstrated to be safe in a non-endemic population. [19].

Furthermore, the antigen specific nature of the rapid diagnostic testing can be useful in areas where both *Babesia* species are endemic and/or babesiosis is suspected based upon epidemiologic exposure (e.g. in the setting of a tick bite in a recently returned traveler). There is no antigenic cross-reactivity between the malaria antigens used in rapid diagnostic testing and babesia; therefore, a patient with intra-erythrocytic parasites on smear who has a negative rapid diagnostic test is quite likely to have babesia.

Species Difference: Clinical Considerations

For the generalist, the largest distinction in smear microscopy should be made between infections with *Plasmodium falciparum* and non-falciparum species. *P. falciparum* is responsible for the majority of imported disease, is associated with more severe disease (see section below), and requires treatment different from the other species. Furthermore, occasionally other bloodborne parasites are observed and smear microscopy should be considered to look for other types of bloodstage parasitic infections in the febrile patient returning from an area where malaria is endemic. Even in centers with ready access to rapid molecular diagnostics, we would recommend that all patients with suspected or confirmed malaria receive a peripheral smear.

Caution should be advised, as mixed infections can happen in most areas of the world. Even in areas with experienced microscopists, 10% of patients diagnosed with *Plasmodium vivax* infections (associated with less severe disease) actually have *Plasmodium falciparum* when compared with the reference standard of PCR-based species identification [20] In general, *Plasmodium falciparum* typically has mostly ring stages in peripheral smear (Figure 3).

Treatment

- **seek expert opinion**
- **consider inpatient admission and treat as sepsis syndrome**
- **artemesin based compounds are standard of care but not always readily available**
- **for severe infection, initiate treatment with quinidine while awaiting further guidance**

Treatment of malaria is beyond the scope of this manuscript. For the clinician unfamiliar with malaria, we advise seeking expert advice immediately upon making a diagnosis of malaria. The CDC maintains an active hotline with excellent clinical advice available 24 hours a day. The number is **770-488-7100**. In general, we recommend inpatient admission for any patient diagnosed with malaria until the clinical course is clear and the patient stabilized. This is because malaria can cause rapid clinical decline including both respiratory distress from acute lung injury and respiratory depression from cerebral malaria. Therefore, the ready availability of critical care resources can be lifesaving.

Although non-falciparum malaria is generally treatable with chloroquine, the consequences of treating drug-resistant falciparum malaria this way can be grave. Thus, if there is any doubt whatsoever regarding the species involved, treat presumptively for falciparum.

In general, artemisinin based compounds are recommended as the standard of care for falciparum malaria. This is because these drugs rapidly kill all stages of the parasite, and clinical trials in endemic populations have demonstrated mortality benefit when compared to intravenous quinine. The problem is that these compounds may not be readily available at all centers. Uncomplicated malaria can be treated with oral artemether-lumefantrine or atovaquone-proguanil or quinine + doxycycline, whereas complicated or severe malaria should be treated in the ICU with parenteral artesunate or quinidine plus clindamycin or doxycycline. Time is of the essence in treating malaria, and therefore we recommend initiating treatment immediately with any effective anti-falciparum compound available while seeking expert consultation. In our experience, parenteral quinidine is more commonly available because of its utility as an antiarrhythmic.

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Key points

- “Medications for Malaria chemoprophylaxis work well, and choice of agent is largely dependent on cost and side effects”
- “There can be a long lag-time between acquisition of the malaria parasite and development of disease (months).”
- “Cyclical fevers are NOT characteristic of malaria, and many patients present with gastrointestinal disease”
- “Rapid diagnostic tests are as sensitive as classic blood smears, but do not depend on experienced microscopists”
- “In patients from non-endemic areas who return with malaria, it should be treated as a sepsis syndrome.”

Figure 1. Malaria Life Cycle

The malaria parasite life cycle involves two hosts. During a blood meal, a malaria-infected female *Anopheles* mosquito inoculates sporozoites into the human host ①. Sporozoites infect liver cells ② and mature into schizonts ③, which rupture and release merozoites ④. (Of note, in *P. vivax* and *P. ovale* a dormant stage [hypnozoites] can persist in the liver and cause relapses by invading the bloodstream weeks, or even years later.) After this initial replication in the liver (exo-erythrocytic schizogony A), the parasites undergo asexual multiplication in the erythrocytes (erythrocytic schizogony B). Merozoites infect red blood cells ⑤. The ring stage trophozoites mature into schizonts, which rupture releasing merozoites ⑧. Some parasites differentiate into sexual erythrocytic stages (gametocytes) ⑦. Blood stage parasites are responsible for the clinical manifestations of the disease. The gametocytes, male (microgametocytes) and female (macrogametocytes), are ingested by an *Anopheles* mosquito during a blood meal ⑩. The parasites' multiplication in the mosquito is known as the sporogonic cycle C. While in the mosquito's stomach, the microgametes penetrate the macrogametes generating zygotes ⑨. The zygotes in turn become motile and elongated (ookinetes) ⑪ which invade the midgut wall of the mosquito where they develop into oocysts ⑫. The oocysts grow, rupture, and release sporozoites ⑬, which make their way to the mosquito's salivary glands. Inoculation of the sporozoites ① into a new human host perpetuates the malaria life cycle.

From Centers for Disease Control and Prevention. About malaria. Available at: <http://www.cdc.gov/malaria/about/biology/>. Last accessed Aug 26 2015; with permission.

Figure 2. Rapid Diagnostic Test for Malaria

Some training is required to perform and interpret this assay, but much less than for blood smears.

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Figure 3. Thin smear of *P.falciparum* malaria

Note high burden of parasites which look like signet rings or headphones within multiply-infected normal-sized erythrocytes, all hallmarks of *P.falciparum*.

Table 1**Malaria Chemoprophylaxis Summary**

Drug	Reasons to consider using this drug	Reasons to consider avoiding this drug
Atovaquone/Proguanil (Malarone)	<ul style="list-style-type: none"> • Good for last-minute travelers because the drug is started 1–2 days before traveling to an area where malaria transmission occurs • Some patients prefer to take a daily medicine • Good choice for shorter trips because it is only taken for 7 days after traveling rather than 4 weeks • Very well tolerated—side effects uncommon • Pediatric tablets are available and may be more convenient 	<ul style="list-style-type: none"> • Cannot be used by women who are pregnant or breastfeeding a child less than 5 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 patients (including children) would rather not take a dose every day
Chloroquine	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Cannot be used in areas with chloroquine or mefloquine resistance • May exacerbate psoriasis • Some patients would rather not take a weekly medication • For trips of short duration, some people would rather not take medication for 4 weeks after travel • Not a good choice for last-minute travelers because drug needs to be started 1–2 weeks prior to travel
Doxycycline	<ul style="list-style-type: none"> • Some people prefer to take a daily medicine • Good for last-minute travelers because the drug is started 1–2 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 	<ul style="list-style-type: none"> • Cannot be used by pregnant women and children <8 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 4 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)	<ul style="list-style-type: none"> • Some patients would rather take medicine weekly • Good choice for long trips because it is taken only weekly • Can be used during pregnancy 	<ul style="list-style-type: none"> • 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

Drug	Reasons to consider using this drug	Reasons to consider avoiding this drug
		<ul style="list-style-type: none">• Not a good choice for last-minute travelers because drug needs to be started at least 2 weeks prior to travel• Some patients would rather not take a weekly medication• For trips of short duration, some people would rather not take medication for 4 weeks after travel

From Centers for Disease Control and Prevention. Choosing a drug to prevent malaria. Available at: <http://www.cdc.gov/malaria/travelers/drugs.html>. Last accessed Aug 26 2015; with permission.